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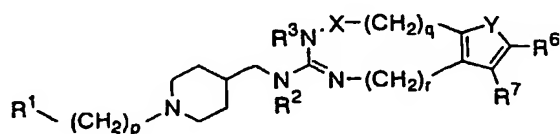
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(54) Title: PIPERIDINE DERIVATIVES HAVING CCR3 ANTAGONISM

(54) 発明の名称: CCR3 拮抗作用を有するピペリジン誘導体



(I)

adducts thereof and medicinal compositions having effects of treating and/or preventing diseases in which CCR3 participates such as asthma and allergic nephritis which contain the same as the active ingredient.

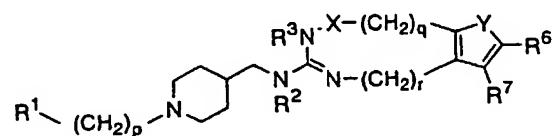
(57) Abstract: It is intended to provide low-molecular weight compounds having an activity of inhibiting the binding of a CCR3 ligand to CCR3 on a target cell, i.e., CCR3 antagonists. Namely, compounds represented by the following general formula (I), pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C<sub>1-6</sub> alkyl

[続葉有]



## (57) 要約:

本発明の目的は、CCR3のリガンドが標的細胞上のCCR3に結合することを阻害する活性を有する低分子化合物、すなわちCCR3拮抗剤を提供することである。本発明は、下記式(I)で表わされる化合物、その薬学的に許容される酸付加体、又はその薬学的に許容されるC<sub>1</sub>～C<sub>6</sub>アルキル付加体、或いはそれを有効成分として含有する、喘息、アレルギー性鼻炎等のCCR3が関与する疾患を治療及び／又は予防する作用を有する医薬組成物である。



(I)

## 明細書

## CCR3拮抗作用を有するペペリジン誘導体

## 技術分野

本発明は、CCR3 (C—C Chemokine Receptor 3) 拮抗作用を有するペペリジン誘導体に関する。さらに詳しくは、本発明は、気管支喘息、アレルギー性鼻炎、アトピー性皮膚炎、蕁麻疹、接触皮膚炎、又はアレルギー性結膜炎等のアレルギー性疾患、潰瘍性大腸炎又はクローン病等の炎症性腸疾患、好酸球増加症、好酸球性胃腸炎、好酸球増加性腸症、好酸球性筋膜炎、好酸球性肉芽腫、好酸球性膿疱性毛包炎、好酸球性肺炎、又は好酸球性白血病等の好酸球、好塩基球、又は活性化T細胞等の増加又は組織への浸潤が病気の進行、維持に主要な役割を演じている疾患、或いはHIV（ヒト免疫不全ウイルス）の感染に起因するエイズ（AIDS：後天性免疫不全症候群）に対する治療薬及び／又は予防薬として効果が期待できるCCR3拮抗剤に関する。

## 背景技術

近年、気管支喘息等のアレルギー性疾患の本質的な病態は慢性炎症であるという概念が確立され、なかでも好酸球の炎症局所への集積がその大きな特徴の一つとしてとらえられている（例えば、Busse, W. W. J. Allergy Clin. Immunol. 1998, 102, S17-S22；藤澤隆夫 現代医療 1999, 31, 1297等参照）。例えば、サルの喘息モデルにおいて抗接着分子（ICAM-1）抗体を投与することにより、好酸球の集積が抑えられ、遅発型の喘息症状発現が抑制されることから、アレルギー性疾患における好酸球

の重要性が強く示唆されている (Wegner, C. D. et al. Science, 1990, 247, 456)。

この好酸球の集積及び／又は遊走を引き起こす特異的走化因子 (好酸球特異的ケモカイン) としてエオタキシンが同定された (例えば、Jose, P. J., et al. J. Exp. Med. 1994, 179, 881; Garcia-Zepeda, E. A. et al. Nature Med. 1996, 2, 449; Ponath, P. D. et al. J. Clin. Invest. 1996, 97, 604; Kitaura, M. et al. J. Biol. Chem. 1996, 271, 7725 等参照)。また、エオタキシンは好酸球上に発現しているCCR3に結合し、好酸球の集積及び／又は遊走の作用を発現することが解明された。さらに、エオタキシン-2、RANTES (regulated upon activation normal T-cell expressed and secretedの略称。)、MCP-2 (monocyte chemoattractant protein-2の略称。)、MCP-3 (monocyte chemoattractant protein-3の略称。)、MCP-4 (monocyte chemoattractant protein-4の略称。) 等の走化性因子もエオタキシンよりも作用強度は弱いものの、CCR3を介してエオタキシンと同様の作用を示し得ることが知られている (例えば、Kitaura, M. et al. J. Biol. Chem. 1996, 271, 7725; Daugherty, B. L. et al. J. Exp. Med. 1996, 183, 2349; Ponath, P. D. et al. J. Exp. Med. 1996, 183, 2437; Hiath, H. et al. J. Clin. Invest. 1997, 99, 178; Patel, V.



P. et al. J. Exp. Med. 1997, 185, 1163 ; Forssmann, U. et al. J. Exp. Med. 185, 2171, 1997等参照)。

エオタキシンの好酸球への作用は、好酸球の遊走惹起のみだけでなく、接着分子受容体 (CD11b) の発現増強 (例えば、Tenscher, K. et al. Blood, 1996, 88, 3195等参照)、活性酸素の産生促進 (例えば、Elsner, J. et al. Eur. J. Immunol. 1996, 26, 1919等参照)、EDN (eosinophil-derived neurotoxin の略称) の放出促進 (El-Shazly, et al. Int. Arch. Allergy Immunol. 1998, 117 (suppl. 1), 55参照) 等、好酸球の活性化に関する作用も報告されている。また、エオタキシンは骨髄からの好酸球及びその前駆細胞の血中への遊離を促進させる作用を有することも報告されている (例えば、Palframan, R. T. et al. Blood 1998, 91, 2240等参照)。

エオタキシン及びCCR3が、気管支喘息等のアレルギー性疾患において重要な役割を演じていることが、多くの報告により示唆されている。例えば、マウス喘息モデルにおいて抗エオタキシン抗体により好酸球浸潤が抑制されること (Gonzalo, J. -A. et al. J. Clin. Invest. 1996, 98, 2332参照)、マウス皮膚アレルギーモデルにおいて抗エオタキシン抗血清により好酸球浸潤が抑制されること (Teixeira, M. M. et al. J. Clin. Invest. 1997, 100, 1657)、マウスモデルにおいて抗エオタキシン抗体が肺肉芽腫の形成を抑制すること (Ruth, J. H. et al. J. Immunol. 1998, 161,

4276参照)、エオタキシン遺伝子欠損マウスを用いた喘息モデル及び間質性角膜炎モデルにおいて好酸球の浸潤が抑制されること(Rotenberg, M. E. et al. J. Exp. Med. 1997, 185, 785参照)、喘息患者の気管支では健常者に比べエオタキシン及びCCR3の発現が、遺伝子レベル、蛋白レベルともに亢進していること(Ying, S. et al. Eur. J. Immunol. 1997, 27, 3507参照)、慢性副鼻腔炎患者の鼻上皮下組織ではエオタキシンの発現が亢進していること(Am. J. Respir. Cell Mol. Biol. 1997, 17, 683参照)等が報告されている。

また、炎症性大腸疾患である潰瘍性大腸炎及びクローン病の炎症部位において、エオタキシンが多く発現していることが報告されていることから(Garcia-Zepeda, E. A. et al. Nature Med. 1996, 2, 449参照)、これらの炎症性腸疾患においてもエオタキシンが重要な役割を担っていることが考えられる。

これらのデータから、エオタキシンは、CCR3を介して好酸球を病変部位に集積、活性化することにより、好酸球が病変の進展に深く関わっていると想定され得る疾患、例えば、気管支喘息、アレルギー性鼻炎、アトピー性皮膚炎、蕁麻疹、接触皮膚炎、又はアレルギー性結膜炎等のアレルギー性疾患、潰瘍性大腸炎又はクローン病等の炎症性腸疾患、或いは好酸球増加症、好酸球性胃腸炎、好酸球増加性腸症、好酸球性筋膜炎、好酸球性肉芽腫、好酸球性膿疱性毛包炎、好酸球性肺炎、又は好酸球性白血病等の発症、進展、又は維持に深く関与していることが強く示唆されている。さらに、CCR3は好酸球のみならず好塩基球、Th2リンパ球上にも発現しており、エオタキシンによりこれらの細胞の細胞内カルシウムイオン濃度上昇及び細胞遊走が惹起されることが報告さ

れていることから、エオタキシン及びCCR3は好塩基球及びTh2リンパ球の細胞を集積させ、活性化する事によってもアレルギー性疾患等、これらの細胞が関与する疾患の発症、進展、又は維持に関わっていると考えられる（例えば、Sallusto, F. et al. Science 1997, 277, 2005; Gerber, B. O. et al. Current Biol. 1997, 7, 836; Sallusto, F. et al. J. Exp. Med. 1998, 187, 875; Uguccioni, M. et al. J. Clin. Invest. 1997, 100, 1137; Yamada, H. et al. Biochem Biophys. Res. Commun. 1997, 231, 365等参照）。

従って、エオタキシン等のCCR3のリガンドがCCR3に結合することを阻害する化合物、すなわち、CCR3拮抗剤は、CCR3のリガンドの標的細胞への作用を阻害するので、アレルギー性疾患又は炎症性腸疾患等の疾患の治療薬及び／又は予防薬として有用であることが期待できる。が、そのような作用を有する薬剤は知られてない。

また、HIV-1（ヒト免疫不全ウイルス-1）が宿主細胞に感染する際にCCR3を利用する可能性のあることが報告されていることから、CCR3拮抗剤はHIVウイルス感染に起因するエイズ（AIDS：後天性免疫不全症候群）の治療薬若しくは予防薬としても有用であることが期待できる（例えば、Choe, H. et al. Cell 1996, 85, 1135; Doranz, B. J. et al. Cell 1996, 85, 1149参照）。

最近、ピペリジン誘導体（WO9802151号明細書、WO9804554号明細書、WO0029377号明細書、WO0031033号明細書、WO0035449号明細書、WO0035451号明細書、

WO 00 3 5 4 5 2号明細書、WO 00 3 5 4 5 3号明細書、WO 00 3 5 4 5 4号明細書、WO 00 3 5 8 7 6号明細書、WO 00 3 5 8 7 7号明細書、WO 00 5 1 6 0 7号明細書、WO 00 5 1 6 0 8号明細書、WO 00 5 1 6 0 9号明細書、WO 00 5 1 6 1 0号明細書、WO 00 5 3 6 0 0号明細書、WO 00 5 8 3 0 5号明細書、WO 00 5 9 4 9 7号明細書、WO 00 5 9 4 9 8号明細書、WO 00 5 9 5 0 2号明細書、WO 00 5 9 5 0 3号明細書、WO 00 7 6 5 1 1号明細書、WO 00 7 6 5 1 2号明細書、WO 00 7 6 5 1 3号明細書、WO 00 7 6 5 1 4号明細書、WO 00 7 6 9 7 2号明細書、WO 00 7 6 9 7 3号明細書、WO 01 0 5 7 8 2号明細書、WO 01 1 4 3 3 3号明細書、WO 01 6 4 2 1 6号明細書、WO 01 7 7 1 0 1号明細書、WO 01 9 2 2 2 7号明細書、WO 01 9 8 2 6 8号明細書、WO 01 9 8 2 6 9号明細書、WO 01 9 8 2 7 0号明細書、WO 02 0 2 5 2 5号明細書、WO 02 0 4 4 2 0号明細書参照)、ピペラジン誘導体 (EP 0 9 0 3 3 4 9号明細書、WO 00 3 4 2 7 8号明細書、WO 01 0 2 3 8 1号明細書参照)、及びその他の低分子化合物 (WO 9 9 5 5 3 2 4号明細書、WO 9 9 5 5 3 3 0号明細書、WO 00 0 4 0 0 3号明細書、WO 00 2 7 8 0 0号明細書、WO 00 2 7 8 3 5号明細書、WO 00 2 7 8 4 3号明細書、WO 00 3 1 0 3 2号明細書、WO 00 4 1 6 8 5号明細書、WO 00 5 3 1 7 2号明細書、WO 01 0 9 0 8 8号明細書、WO 01 2 8 9 8 7号明細書、WO 01 2 9 0 0 0号明細書参照) が、CCR 3に対する拮抗活性を有することが報告されている。しかしながら、これらの化合物は、本発明の化合物とは異なる。

WO 01 0 7 4 3 6号明細書及びWO 9 9 3 7 3 0 4号明細書には、ファクターX a阻害活性を有するオキシピペラジン誘導体が記載されているが、本発明のピペリジン誘導体に関する具体的記載はなく、またこ

これらのオキソピペラジン誘導体がCCR3拮抗阻害活性を有することは知られていない。WO 0132615号明細書及びWO 0268409号明細書には、NMDA/NR2B拮抗活性を有するN-置換ピペリジン誘導体が記載されているが、本発明のピペリジン誘導体に関する具体的記載はなく、これらのN-置換ピペリジン誘導体がCCR3拮抗阻害活性を有することは知られていない。

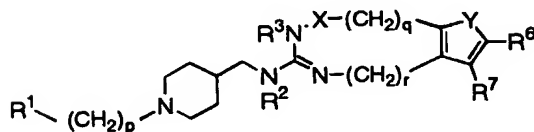
本発明の目的は、CCR3のリガンドが標的細胞上のCCR3に結合することを阻害する活性を有する低分子化合物、すなわちCCR3拮抗剤を提供することである。

本発明の更なる目的は、CCR3のリガンドが標的細胞上のCCR3に結合することが病因の一つである疾患の治療剤及び／又は予防剤を提供することである。

#### 発明の開示

本発明は、

(1) 式(I)



(I)

[式中、 $R^1$ はフェニル基、 $C_3 \sim C_8$ シクロアルキル基、又は芳香族複素環基（ヘテロ原子として酸素原子、硫黄原子、及び窒素原子からなる群から選ばれる原子を1～3個有する。）を表わし、

$R^1$ におけるフェニル基又は芳香族複素環基は、ベンゼン環又は芳香族複素環基（ヘテロ原子として酸素原子、硫黄原子、及び窒素原子からなる群から選ばれる原子を1～3個有する。）と縮合して縮合環を形成し

てもよく、

$R^1$ におけるフェニル基、 $C_3 \sim C_8$ シクロアルキル基、芳香族複素環基、又は縮合環は、無置換或いはハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、カルボキシ基、 $C_1 \sim C_6$ アルキル基、 $C_3 \sim C_8$ シクロアルキル基、 $C_2 \sim C_6$ アルケニル基、 $C_1 \sim C_6$ アルコキシ基、 $C_1 \sim C_6$ アルキルチオ基、 $C_3 \sim C_5$ アルキレン基、 $C_2 \sim C_4$ アルキレンオキシ基、 $C_1 \sim C_3$ アルキレンジオキシ基、フェニル基、フェノキシ基、フェニルチオ基、ベンジル基、ベンジルオキシ基、ベンゾイルアミノ基、ホルミル基、 $C_2 \sim C_7$ アルカノイル基、 $C_2 \sim C_7$ アルコキシカルボニル基、 $C_2 \sim C_7$ アルカノイルオキシ基、 $C_2 \sim C_7$ アルカノイルアミノ基、 $C_1 \sim C_6$ アルキルスルホニル基、 $C_3 \sim C_8$ （アルコキシカルボニル）メチル基、アミノ基、モノ（ $C_1 \sim C_6$ アルキル）アミノ基、ジ（ $C_1 \sim C_6$ アルキル）アミノ基、カルバモイル基、 $C_2 \sim C_7$ N-アルキルカルバモイル基、 $C_4 \sim C_9$ N-シクロアルキルカルバモイル基、N-フェニルカルバモイル基、ピペリジルカルボニル基、モルホリニルカルボニル基、ピロリジニルカルボニル基、ピペラジニルカルボニル基、N-メトキシカルバモイル基、（ホルミル）アミノ基、及びウレイド基からなる群から選ばれる1個以上の置換基で置換されてもよく、

$R^1$ のフェニル基、 $C_3 \sim C_8$ シクロアルキル基、芳香族複素環基、又は縮合環の置換基は、無置換或いは $C_1 \sim C_6$ アルキル基、 $C_2 \sim C_6$ アルケニル基、 $C_2 \sim C_6$ アルキニル基、フェニル基、 $C_3 \sim C_5$ アルキレン基、 $C_3 \sim C_8$ シクロアルキル基、 $C_3 \sim C_8$ シクロアルケニル基、 $C_1 \sim C_6$ アルコキシ基、 $C_1 \sim C_6$ アルキルチオ基、アミノ基、モノ（ $C_1 \sim C_6$ アルキル）アミノ基、ジ（ $C_1 \sim C_6$ アルキル）アミノ基、ピロリジニル基、ピペリジル基、 $C_3 \sim C_7$ ラクタム基、カルバモイル基、 $C_2 \sim C_7$ N-アルキルカルバモイル基、 $C_2 \sim C_7$ アルコキシカルボニル基、

カルボキシル基、ヒドロキシ基、ベンゾイル基、シアノ基、トリフルオロメチル基、ハロゲン原子、及び *tert*-ブトキシカルボニルアミノ基からなる群から選ばれる 1 個以上の置換基によって置換されていてもよい。

ただし、 $R^1$  が  $C_3 \sim C_8$  シクロアルキル基の場合、その置換基としてアミノ基、モノ ( $C_1 \sim C_6$  アルキル) アミノ基、又はジ ( $C_1 \sim C_6$  アルキル) アミノ基を含まない。

$p$  は、1 ~ 6 の整数を表す。

$R^2$  及び  $R^3$  は、同一又は異なって、それぞれ独立に、水素原子、 $C_1 \sim C_6$  アルキル基、又はフェニル基を表わし、

$R^2$  及び  $R^3$  における  $C_1 \sim C_6$  アルキル基又はフェニル基は、無置換或いはハロゲン原子、ヒドロキシ基、 $C_1 \sim C_6$  アルキル基、 $C_2 \sim C_7$  アルコキシカルボニル基、アミノ基、カルバモイル基、カルボキシル基、シアノ基、及び  $C_1 \sim C_6$  アルコキシ基からなる群から選ばれる 1 個以上の置換基によって置換されてもよい。

$X$  は、 $-CO-$ 、 $-SO_2-$ 、 $-CH_2-$ 、 $-CS-$ 、又は単結合を表す。

$q$  は、0 又は 1 を表す。

$r$  は、0 又は 1 を表す。

$Y$  は、 $-(R^4)C=C(R^5)-$ 、 $-S-$ 、又は  $-NR^8-$  を表す。

$R^4$ 、 $R^5$ 、 $R^6$  及び  $R^7$  は、同一又は異なって、それぞれ独立に、水素原子、ハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、カルボキシル基、 $C_1 \sim C_6$  アルキル基、 $C_3 \sim C_8$  シクロアルキル基、 $C_2 \sim C_6$  アルケニル基、 $C_1 \sim C_6$  アルコキシ基、 $C_1 \sim C_6$  アルキルチオ基、 $C_3 \sim C_5$  アルキレン基、 $C_2 \sim C_4$  アルキレンオキシ基、 $C_1 \sim C_3$  アルキレンジオキシ基、フェニル基、フェノキシ基、フェニルチオ基、フェニ

ルスルフォニル基、ベンジル基、ベンジルオキシ基、ベンゾイルアミノ基、ホルミル基、 $C_2 \sim C_7$ アルカノイル基、 $C_2 \sim C_7$ アルコキシカルボニル基、 $C_2 \sim C_7$ アルカノイルオキシ基、 $C_2 \sim C_7$ アルカノイルアミノ基、 $C_4 \sim C_{10}$ シクロアルカノイルアミノ基、 $C_3 \sim C_7$ アルケノイルアミノ基、 $C_1 \sim C_6$ アルキルスルホニル基、 $C_1 \sim C_6$ アルキルスルホニルアミノ基、 $C_3 \sim C_8$ （アルコキシカルボニル）メチル基、アミノ基、モノ（ $C_1 \sim C_6$ アルキル）アミノ基、ジ（ $C_1 \sim C_6$ アルキル）アミノ基、カルバモイル基、 $C_2 \sim C_7$ N-アルキルカルバモイル基、 $C_4 \sim C_9$ N-シクロアルキルカルバモイル基、N-フェニルカルバモイル基、N-（ $C_7 \sim C_{12}$ フェニルアルキル）カルバモイル基、ピペリジルカルボニル基、モルホリニルカルボニル基、ピロリジニルカルボニル基、ピペラジニルカルボニル基、N-メトキシカルバモイル基、スルファモイル基、 $C_1 \sim C_6$ N-アルキルスルファモイル基、（ホルミル）アミノ基、（チオホルミル）アミノ基、ウレイド基、又はチオウレイド基を表し、

$R^4$ 、 $R^5$ 、 $R^6$ 及び $R^7$ の前記基は、それぞれ独立に、無置換或いは $C_1 \sim C_6$ アルキル基、 $C_2 \sim C_6$ アルケニル基、 $C_2 \sim C_6$ アルキニル基、フェニル基、 $C_3 \sim C_5$ アルキレン基、 $C_3 \sim C_8$ シクロアルキル基、 $C_3 \sim C_8$ シクロアルケニル基、 $C_1 \sim C_6$ アルコキシ基、（ $C_1 \sim C_6$ アルコキシ）（ $C_1 \sim C_6$ アルコキシ）基、フェニル（ $C_1 \sim C_6$ アルコキシ）基、 $C_1 \sim C_6$ アルキルチオ基、アミノ基、モノ（ $C_1 \sim C_6$ アルキル）アミノ基、ジ（ $C_1 \sim C_6$ アルキル）アミノ基、ピロリジニル基、ピペリジル基、（ $C_2 \sim C_7$ アルカノイル）ピペリジル基、 $C_3 \sim C_7$ ラクタム基、カルバモイル基、 $C_2 \sim C_7$ N-アルキルカルバモイル基、 $C_4 \sim C_9$ N-シクロアルキルカルバモイル基、N-フェニルカルバモイル基、N-（ $C_7 \sim C_{12}$ フェニルアルキル）カルバモイル基、 $C_2 \sim$



C<sub>7</sub>アルカノイルアミノ基、C<sub>2</sub>～C<sub>7</sub>アルコキシカルボニル基、カルボキシル基、ヒドロキシ基、ベンゾイル基、シアノ基、トリフルオロメチル基、ハロゲン原子、tert-ブトキシカルボニルアミノ基、C<sub>1</sub>～C<sub>6</sub>アルキルスルホニル基、及び複素環若しくは芳香族複素環（複素環若しくは芳香族複素環は、ヘテロ原子として酸素原子、硫黄原子、及び窒素原子からなる群から選ばれる原子を1～3個有し、C<sub>1</sub>～C<sub>6</sub>アルキル基で置換されてもよい。）からなる群から選ばれる1個以上の置換基によって置換されていてもよい。

R<sup>8</sup>は、水素原子又はC<sub>1</sub>～C<sub>6</sub>アルキル基を表わし、

R<sup>8</sup>におけるC<sub>1</sub>～C<sub>6</sub>アルキル基は、無置換或いはハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、カルボキシル基、カルバモイル基、メルカプト基、グアニジノ基、C<sub>3</sub>～C<sub>8</sub>シクロアルキル基、C<sub>1</sub>～C<sub>6</sub>アルコキシ基、C<sub>1</sub>～C<sub>6</sub>アルキルチオ基、フェニル基（フェニル基は、無置換或いはハロゲン原子、ヒドロキシ基、C<sub>1</sub>～C<sub>6</sub>アルキル基、C<sub>1</sub>～C<sub>6</sub>アルコキシ基、及びベンジルオキシ基からなる群から選ばれる1個以上の置換基によって置換されていてもよい。）、フェノキシ基、ベンジルオキシ基、ベンジルオキシカルボニル基、C<sub>2</sub>～C<sub>7</sub>アルカノイル基、C<sub>2</sub>～C<sub>7</sub>アルコキシカルボニル基、C<sub>2</sub>～C<sub>7</sub>アルカノイルオキシル基、C<sub>2</sub>～C<sub>7</sub>アルカノイルアミノ基、C<sub>2</sub>～C<sub>7</sub>N-アルキルカルバモイル基、C<sub>2</sub>～C<sub>6</sub>アルキルスルホニル基、アミノ基、モノ（C<sub>1</sub>～C<sub>6</sub>アルキル）アミノ基、ジ（C<sub>1</sub>～C<sub>6</sub>アルキル）アミノ基、及びウレイド基からなる群から選ばれる1個以上の置換基によって置換されていてもよい。]

で表される化合物、その薬学的に許容される酸付加体、又はその薬学的に許容されるC<sub>1</sub>～C<sub>6</sub>アルキル付加体、

（2）前記式（I）において、Xが-SO<sub>2</sub>-である（1）に記載の化

合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(3) 前記式 (I) において、X が  $-CO-$  である (1) に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(4) 前記式 (I) において、X が  $-CH_2-$  である (1) に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(5) 前記式 (I) において、X が  $-CS-$  である (1) に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(6) 前記式 (I) において、X が単結合である (1) に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(7) 前記式 (I) において、Y が  $-(R^4)C=C(R^5)-$  である (1) ~ (6) のいずれかに記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(8) 前記式 (I) において、Y が  $-S-$  である (1) ~ (6) のいずれかに記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(9) 前記式 (I) において、Y が  $-NR^8-$  である (1) ~ (6) のいずれかに記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(10) 前記式 (I) において、 $R^1$  が置換もしくは無置換のフェニル基である (1) ~ (9) のいずれかに記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加

体、

(11) 前記式 (I) において、 $R^2$  が水素原子である (1) ~ (10) のいずれかに記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(12) 前記式 (I) において、 $R^3$  が水素原子である (1) ~ (11) のいずれかに記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(13) 前記式 (I) において、 $q = 0$  であり、かつ  $r = 0$  である (1) ~ (12) のいずれかに記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(14) 前記式 (I) において、 $q = 1$  であり、かつ  $r = 0$  である (1) ~ (12) のいずれかに記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(15) 前記式 (I) において、 $q = 0$  であり、かつ  $r = 1$  である (1) ~ (12) のいずれかに記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(16) 前記式 (I) において、 $p = 1$  である (1) ~ (15) のいずれかに記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(17) 前記式 (I) において、 $Y$  が  $-(R^4)C=C(R^5)-$  であり、 $R^1$  が置換もしくは無置換のフェニル基であり、 $R^2$  が水素原子であり、 $R^3$  が水素原子であり、 $q = 0$  であり、 $r = 0$  であり、 $p = 1$  である (2) に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体、

(18) 前記式 (I) において、 $Y$  が  $-(R^4)C=C(R^5)-$  であり、 $R^1$  が置換もしくは無置換のフェニル基であり、 $R^2$  が水素原子で

あり、 $R^3$ が水素原子であり、 $q = 0$ であり、 $r = 0$ であり、 $p = 1$ である(3)に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体。

(19) 前記式(I)において、Yが $-(R^4)C=C(R^5)-$ であり、 $R^1$ が置換もしくは無置換のフェニル基であり、 $R^2$ が水素原子であり、 $R^3$ が水素原子であり、 $q = 0$ であり、 $r = 0$ であり、 $p = 1$ である(4)に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体、

(20) 前記式(I)において、Yが $-(R^4)C=C(R^5)-$ であり、 $R^1$ が置換もしくは無置換のフェニル基であり、 $R^2$ が水素原子であり、 $R^3$ が水素原子であり、 $q = 0$ であり、 $r = 0$ であり、 $p = 1$ である(6)に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体、

(21) 前記式(I)において、 $R^4$ 及び $R^5$ が、同一または異なって、それぞれ独立に、水素原子、ハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、カルボキシ基、 $C_1 \sim C_6$ アルキル基、 $C_1 \sim C_6$ アルコキシ基、 $C_2 \sim C_7$ アルコキシカルボニル基、 $C_2 \sim C_7$ アルカノイルアミノ基、 $C_1 \sim C_6$ アルキルスルホニル基、アミノ基、カルバモイル基、 $C_2 \sim C_7$ N-アルキルカルバモイル基、スルファモイル基、又は $C_1 \sim C_6$ N-アルキルスルファモイル基である(17)～(20)のいずれかに記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体、

(22) 前記式(I)において、 $R^4$ 及び $R^5$ が、同一または異なって、それぞれ独立に、ハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、 $C_1 \sim C_6$ アルキル基、 $C_1 \sim C_6$ アルコキシ基、 $C_2 \sim C_7$ アルコキシカルボニル基、 $C_1 \sim C_6$ アルキルスルホニル基、又は $C_1 \sim C_6$ N-アル

キルスルファモイル基、である(17)～(20)のいずれかに記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体、

(23) 前記式(I)において、 $R^1$ が、同一または異なって、それぞれ独立に水素原子、ハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、 $C_1 \sim C_6$ アルキル基、又は $C_1 \sim C_6$ アルコキシ基である(17)～(22)のいずれかに記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体。

(24) (1)～(23)のいずれかに記載の前記式(I)で表される化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体を有効成分とする、CCR3拮抗作用を有する医薬組成物、

(25) (1)～(23)のいずれかに記載の前記式(I)で表される化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体を有効成分とする、CCR3が関与する疾患の予防及び／又は治療用組成物、

(26) 前記疾患がアレルギー性疾患である(25)に記載の予防及び／又は治療用組成物、

(27) 前記アレルギー性疾患が、気管支喘息、アレルギー性鼻炎、アトピー性皮膚炎、蕁麻疹、接触皮膚炎、又はアレルギー性結膜炎である(26)に記載の予防及び／又は治療用組成物、

(28) 前記疾患が、炎症性腸疾患である(25)に記載の予防及び／又は治療用組成物、

(29) 前記疾患が、エイズ(後天性免疫不全症候群)である(25)に記載の予防及び／又は治療用組成物、

(30) 前記疾患が、好酸球増加症、好酸球性胃腸炎、好酸球増加性腸

症、好酸球性筋膜炎、好酸球性肉芽腫、好酸球性膿疱性毛包炎、好酸球性肺炎、又は好酸球性白血病である（25）に記載の予防及び／又は治療用組成物、である。

#### 発明を実施するための最良の形態

本発明の $R^1$ におけるフェニル基、 $C_3 \sim C_8$ シクロアルキル基、芳香族複素環基、又は縮合環の置換基の数、及び $R^1$ のフェニル基、 $C_3 \sim C_8$ シクロアルキル基、芳香族複素環基、又は縮合環の置換基のさらなる置換基の数は、化学的に可能と考え得る数であり、好ましくは0～15個、より好ましくは0～10個、さらにより好ましくは0～7個である。

$R^1$ における「 $C_3 \sim C_8$ シクロアルキル基」とは、例えばシクロプロピル、シクロブチル、シクロペンチル、シクロヘキシル、シクロヘプチル、及びシクロオクチル基等の環状のアルキル基を意味し、その好適な具体例としては、シクロプロピル基、シクロペンチル基、及びシクロヘキシル基等が挙げられる。

$R^1$ における、「芳香族複素環基（ヘテロ原子として酸素原子、硫黄原子、及び窒素原子からなる群から選ばれる原子を1～3個有する。）」とは、例えば、チエニル、フリル、ピロリル、イミダゾリル、ピラゾリル、オキサゾリル、イソオキサゾリル、チアゾリル、イソチアゾリル、ピリジル、ピリミジニル、トリアジニル、トリアゾリル、オキサジアゾリル（フラザニル）、及びチアジアゾリル基等の芳香族複素環基を意味し、その好適な具体例としては、チエニル、フリル、ピロリル、及びピリジル基等が挙げられる。

$R^1$ における「縮合環」とは、上記フェニル基又は芳香族複素環基が

、ベンゼン環、又は芳香族複素環基（ヘテロ原子として酸素原子、硫黄原子、及び窒素原子からなる群から選ばれる原子を1～3個有する。）と可能な任意の位置で縮合して形成される2環式芳香族複素環基を意味し、その好適な具体例としては、ナフチル、インドリル、ベンゾフラニル、ベンゾチエニル、キノリル及びベンゾイミダゾリル基等が挙げられる。

本発明の $R^1$ は、フェニル基、チエニル基、フラニル基、ピロリル基、ナフチル基、ベンゾチエニル基、ベンゾフラニル基、又はインドリル基である場合が特に好ましい。

$R^1$ におけるフェニル基、 $C_3 \sim C_8$ シクロアルキル基、芳香族複素環基、又は縮合環の置換基としての「ハロゲン原子」とは、フッ素原子、塩素原子、臭素原子、及びヨウ素原子等を意味し、その好適な具体例としてはフッ素原子、塩素原子、臭素原子、又はヨウ素原子が挙げられる。

$R^1$ の置換基としての「 $C_1 \sim C_8$ アルキル基」とは、例えば、メチル、エチル、 $n$ -プロピル、 $n$ -ブチル、 $n$ -ペンチル、 $n$ -ヘキシル、 $n$ -ヘプチル、 $n$ -オクチル、イソプロピル、イソブチル、 $sec$ -ブチル、 $tert$ -ブチル、イソペンチル、ネオペンチル、 $tert$ -ペンチル、イソヘキシル、2-メチルペンチル、及び1-エチルブチル基等の $C_1 \sim C_8$ の直鎖又は分枝状のアルキル基を意味し、その好適な具体例としては、メチル、エチル、プロピル、及びイソプロピル基等が挙げられる。

$R^1$ の置換基としての「 $C_3 \sim C_8$ シクロアルキル基」は、前記 $R^1$ の「 $C_3 \sim C_8$ シクロアルキル基」の定義と同様であり、その好適な具体例も同じ基を挙げることができる。

$R^1$ の置換基としての「 $C_2 \sim C_6$ アルケニル基」とは、例えば、ビニ

ル、アリル、1-プロペニル、2-ブテニル、3-ブテニル、2-メチル-1-プロペニル、4-ペンテニル、5-ヘキセニル、及び4-メチル-3-ペンテニル基等の $C_2 \sim C_6$ の直鎖又は分枝状のアルケニル基を意味し、その好適な具体例としては、ビニル基及び2-メチル-1-プロペニル基等が挙げられる。

$R^1$ の置換基としての「 $C_1 \sim C_6$ アルコキシ基」とは、前記 $C_1 \sim C_6$ アルキル基とオキシ基とからなる基を意味し、その好適な具体例としては、メトキシ基及びエトキシ基等が挙げられる。

$R^1$ の置換基としての「 $C_1 \sim C_6$ アルキルチオ基」とは、前記 $C_1 \sim C_6$ アルキル基とチオ基とからなる基を意味し、その好適な具体例としては、メチルチオ基及びエチルチオ基等が挙げられる。

$R^1$ の置換基としての「 $C_3 \sim C_5$ アルキレン基」とは、例えば、トリメチレン、テトラメチレン、ペンタメチレン、及び1-メチルトリメチレン基等の $C_3 \sim C_5$ の2価のアルキレン基を意味し、その好適な具体例としては、トリメチレン基及びテトラメチレン基等が挙げられる。

$R^1$ の置換基としての「 $C_2 \sim C_4$ アルキレンオキシ基」とは、例えば、エチレンオキシ( $-CH_2CH_2O-$ )、トリメチレンオキシ( $-CH_2CH_2CH_2O-$ )、テトラメチレンオキシ( $-CH_2CH_2CH_2CH_2O-$ )、1,1-ジメチルエチレンオキシ( $-CH_2C(CH_3)_2O-$ )基等の $C_2 \sim C_4$ の2価アルキレン基とオキシ基とからなる基を意味し、その好適な具体例としては、エチレンオキシ基及びトリメチレンオキシ基等が挙げられる。

$R^1$ の置換基としての「 $C_1 \sim C_3$ アルキレンジオキシ基」とは、例えば、メチレンジオキシ( $-OCH_2O-$ )、エチレンジオキシ( $-OCH_2CH_2O-$ )、トリメチレンジオキシ( $-OCH_2CH_2CH_2O-$ )、プロピレンジオキシ( $-OCH_2CH(CH_3)O-$ )基等の $C_1$



～C<sub>3</sub>の2価アルキレン基と2個のオキシ基とからなる基を意味し、その好適な具体例としては、メチレンジオキシ基及びエチレンジオキシ基等が挙げられる。

R<sup>1</sup>の置換基としての「C<sub>2</sub>～C<sub>7</sub>アルカノイル基」とは、例えば、アセチル、プロパノイル、ブタノイル、ペンタノイル、ヘキサノイル、ヘプタノイル、イソブチリル、3-メチルブタノイル、2-メチルブタノイル、ピバロイル、4-メチルペンタノイル、3,3-ジメチルブタノイル、及び5-メチルヘキサノイル基等のC<sub>2</sub>～C<sub>7</sub>の直鎖又は分枝状のアルカノイル基を意味し、その好適な具体例としては、アセチル基等が挙げられる。

R<sup>1</sup>の置換基としての「C<sub>2</sub>～C<sub>7</sub>アルコキシカルボニル基」とは、前記C<sub>1</sub>～C<sub>8</sub>アルコキシ基とカルボニル基とからなる基を意味し、その好適な具体例としては、メトキシカルボニル基及びエトキシカルボニル基等が挙げられる。

R<sup>1</sup>の置換基としての「C<sub>2</sub>～C<sub>7</sub>アルカノイルオキシ基」とは、前記C<sub>2</sub>～C<sub>7</sub>アルカノイル基とオキシ基とからなる基を意味し、その好適な具体例としてはアセチルオキシ基等が挙げられる。

R<sup>1</sup>の置換基としての「C<sub>2</sub>～C<sub>7</sub>アルカノイルアミノ基」とは、前記C<sub>2</sub>～C<sub>7</sub>アルカノイル基とアミノ基とから成る基を意味し、その好適な具体例としては、アセチルアミノ基等が挙げられる。

R<sup>1</sup>の置換基としての「C<sub>1</sub>～C<sub>8</sub>アルキルスルホニル基」とは、前記C<sub>1</sub>～C<sub>8</sub>アルキル基とスルホニル基とからなる基を意味し、その好適な具体例としては、メチルスルホニル基等が挙げられる。

R<sup>1</sup>の置換基としての「C<sub>3</sub>～C<sub>8</sub>（アルコキシカルボニル）メチル基」とは、前記C<sub>2</sub>～C<sub>7</sub>アルコキシカルボニル基とメチル基とからなる基を意味し、その好適な具体例としては、（メトキシカルボニル）メ

チル基及び（エトキシカルボニル）メチル基等が挙げられる。

R<sup>1</sup>の置換基としての「モノ（C<sub>1</sub>～C<sub>6</sub>アルキル）アミノ基」とは、前述したC<sub>1</sub>～C<sub>6</sub>アルキル基によって置換されたアミノ基を意味し、その好適な具体例としては、メチルアミノ基、エチルアミノ基等が挙げられる。

R<sup>1</sup>の置換基としての「ジ（C<sub>1</sub>～C<sub>6</sub>アルキル）アミノ基」とは、同一又は異なった2つの前述したC<sub>1</sub>～C<sub>6</sub>アルキル基によって置換されたアミノ基を意味し、その好適な具体例としては、ジメチルアミノ基、ジエチルアミノ基、及びN-エチル-N-メチルアミノ基等が挙げられる。

R<sup>1</sup>の置換基としての「C<sub>2</sub>～C<sub>7</sub>N-アルキルカルバモイル基」とは、前述したC<sub>1</sub>～C<sub>6</sub>アルキル基とカルバモイル基とからなる基を意味し、その好適な具体例としては、N-メチルカルバモイル基及びN-エチルカルバモイル基等が挙げられる。

R<sup>1</sup>の置換基としての「C<sub>4</sub>～C<sub>9</sub>N-シクロアルキルカルバモイル基」とは、前記C<sub>3</sub>～C<sub>8</sub>シクロアルキル基とカルバモイル基とからなる基を意味し、その好適な具体例としては、N-シクロベンチルカルバモイル基及びN-シクロヘキシルカルバモイル基等が挙げられる。

R<sup>1</sup>の置換基としての「ピペリジルカルボニル基」とは、ピペリジンとカルボニルが結合した基を意味し、好適な具体例としては（1-ピペリジル）カルボニル基等が挙げられる。

R<sup>1</sup>の置換基としての「モルホリニルカルボニル基」とは、モルホリンとカルボニルが結合した基を意味し、好適な具体例としては（1-モルホリニル）カルボニル基等が挙げられる。

R<sup>1</sup>の置換基としての「ピロリジニルカルボニル基」とは、ピロリジンとカルボニルが結合した基を意味し、好適な具体例としては（1-ピ

ロリジニル)カルボニル基等が挙げられる。

$R^1$ の置換基としての「ピペラジニルカルボニル基」とは、ピペラジンとカルボニルが結合した基を意味し、好適な具体例としては(1-ピペラジニル)カルボニル基等が挙げられる。

また、 $R^1$ の置換基として特に好ましいのは、ハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、 $C_1 \sim C_6$ アルキル基、 $C_1 \sim C_6$ アルコキシ基が挙げられる。

$R^1$ のフェニル基、 $C_3 \sim C_8$ シクロアルキル基、芳香族複素環基、又は縮合環の置換基のさらなる置換基としての「 $C_2 \sim C_6$ アルキニル基」とは、例えば、エチニル、メチルエチニル、及びエチルエチニル基等の $C_2 \sim C_6$ アルキニル基を意味し、その好適な具体例としては、エチニル基等が挙げられる。

$R^1$ の置換基のさらなる置換基としての「 $C_3 \sim C_8$ シクロアルケニル基」とは、例えば、シクロペンテニル、シクロヘキセニル、1,3-シクロヘキサジエニル基等の $C_3 \sim C_8$ の環状のアルケニル基を意味し、その好適な具体例としては、シクロヘキセニル基等が挙げられる。

$R^1$ の置換基のさらなる置換基としての「 $C_3 \sim C_7$ ラクタム基」とは、例えば、3-プロパンラクタム、4-ブタンラクタム、5-ペントンラクタム、6-ヘキサンラクタム等の環状アミドから水素原子を1個除いた基を意味し、その好適な具体例としては「4-ブタンラクタムから水素原子を1個除いた基」等が挙げられる。

$R^1$ の置換基のさらなる置換基としての $C_1 \sim C_6$ アルキル基、 $C_2 \sim C_6$ アルケニル基、 $C_1 \sim C_6$ アルコキシ基、 $C_1 \sim C_6$ アルキルチオ基、 $C_3 \sim C_5$ アルキレン基、 $C_3 \sim C_8$ シクロアルキル基、モノ( $C_1 \sim C_6$ アルキル)アミノ基、ジ( $C_1 \sim C_6$ アルキル)アミノ基、 $C_2 \sim C_7$ アルコキシカルボニル基、又は $C_2 \sim C_7$ N-アルキルカルバモイル基は、

$R^1$ の置換基についてそれぞれ定義されたものと同様であり、それぞれ同じ例を好適な具体例として挙げるができる。

式 (I) において、 $p$  は、1～6の整数を表し、好ましくは1又は3である。

本発明の $R^2$ 及び $R^3$ における $C_1 \sim C_6$ アルキル基又はフェニル基の置換基の数は、化学的に可能と考え得る数であり、好ましくは0～13個、より好ましくは0～10個、さらにより好ましくは0～7個である。

$R^2$ 及び $R^3$ における $C_1 \sim C_6$ アルキル基は、 $R^1$ の置換基として定義されたものと同様であり、同じ例を好適な具体例として挙げるができる。

$R^2$ 及び $R^3$ における $C_1 \sim C_6$ アルキル基又はフェニル基の置換基としてのハロゲン原子、 $C_1 \sim C_6$ アルキル基、 $C_2 \sim C_7$ アルコキシカルボニル基及び $C_1 \sim C_6$ アルコキシ基は、前記 $R^1$ の置換基について定義されたものと同様であり、それぞれ同じ例を好適な具体例として挙げることができる。

式 (I) の $R^2$ 及び $R^3$ は、それぞれ水素原子を表す場合が好ましく、どちらも水素原子を表わす場合が特に好ましい。

式 (I) において、 $X$  は、 $-CO-$ 、 $-SO_2-$ 、 $-CH_2-$ 、 $-CS-$ 、又は単結合を表す。いずれも好適な具体例として挙げるができる。ここで、 $-CO-$ はカルボニル基を、 $-SO_2-$ はスルホニル基を、 $-CS-$ はチオカルボニル基をそれぞれ意味する。

式 (I) において、 $q$  は0又は1を表し、 $r$  は0又は1を表す。好適な具体例として、 $q=0$ かつ $r=0$ 、 $q=1$ かつ $r=0$ 、及び $q=0$ かつ $r=1$ の場合を挙げることができる。

式 (I) において、 $Y$  は、 $-(R^4)C=C(R^5)-$ 、 $-S-$ 、又は $-NR^8-$ を表す。いずれも好適な具体例として挙げることができる。

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本発明の $R^4$ 、 $R^5$ 、 $R^6$ 、及び $R^7$ における上記の基の置換基の数は、化学的に可能と考え得る数であり、好ましくは0～15個、より好ましくは0～10個、さらにより好ましくは0～7個である。

$R^4$ 、 $R^5$ 、 $R^6$ 及び $R^7$ における $C_1\sim C_6$ アルキル基、 $C_3\sim C_8$ シクロアルキル基、 $C_2\sim C_6$ アルケニル基、 $C_1\sim C_6$ アルコキシ基、 $C_1\sim C_6$ アルキルチオ基、 $C_3\sim C_5$ アルキレン基、 $C_2\sim C_4$ アルキレンオキシ基、 $C_1\sim C_3$ アルキレンジオキシ基、 $C_2\sim C_7$ アルカノイル基、 $C_2\sim C_7$ アルコキシカルボニル基、ピペリジルカルボニル基、モルホリニルカルボニル基、ピロリジニルカルボニル基、ピペラジニルカルボニル基、 $C_2\sim C_7$ アルカノイルオキシ基、 $C_2\sim C_7$ アルカノイルアミノ基、 $C_1\sim C_6$ アルキルスルホニル基、 $C_3\sim C_8$ （アルコキシカルボニル）メチル基、モノ（ $C_1\sim C_6$ アルキル）アミノ基、ジ（ $C_1\sim C_6$ アルキル）アミノ基、カルバモイル基、 $C_2\sim C_7$ N-アルキルカルバモイル基、又は $C_4\sim C_9$ N-シクロアルキルカルバモイル基は、 $R^1$ の置換基或いはそれら置換基のさらなる置換基についてそれぞれ定義されたものと同様であり、それぞれ同じ例を好適な具体例として挙げる事ができる。

$R^4$ 、 $R^5$ 、 $R^6$ 及び $R^7$ における「 $C_4\sim C_{10}$ シクロアルカノイルアミノ基」とは、 $C_4\sim C_{10}$ シクロアルカノイル基とアミノ基からなる基を意味し、その好適な具体例は、シクロプロパノイルアミノ、シクロブタノイルアミノ、シクロペンタノイルアミノ、及びシクロヘキサノイルアミノ等が挙げられる。

$R^4$ 、 $R^5$ 、 $R^6$ 、及び $R^7$ における「 $C_3\sim C_7$ アルケノイルアミノ基」とは、 $C_3\sim C_7$ アルケノイル基とアミノ基からなる基を意味し、その好適な具体例はアクリロイル等が挙げられる。

R<sup>4</sup>、R<sup>5</sup>、R<sup>6</sup>、及びR<sup>7</sup>における「C<sub>1</sub>～C<sub>6</sub>アルキルスルホニルアミノ基」とは、C<sub>1</sub>～C<sub>6</sub>アルキルスルホニル基とアミノ基からなる基を意味し、その好適な具体例はメチルスルホニルアミノ、エチルスルホニルアミノ、プロピルスルホニルアミノ、及びブチルスルホニルアミノ等が挙げられる。

R<sup>4</sup>、R<sup>5</sup>、R<sup>6</sup>、及びR<sup>7</sup>における「N-(C<sub>7</sub>～C<sub>12</sub>フェニルアルキル)カルバモイル基」とは、カルバモイル基とC<sub>7</sub>～C<sub>12</sub>フェニルアルキル基からなる基を意味し、その好適な具体例はフェニルメチルカルバモイル及びフェニルエチルカルバモイル等が挙げられる。

R<sup>4</sup>、R<sup>5</sup>、R<sup>6</sup>、及びR<sup>7</sup>における「C<sub>1</sub>～C<sub>6</sub>N-アルキルスルファモイル基」とは、R<sup>1</sup>の置換基としての「C<sub>1</sub>～C<sub>6</sub>アルキル基」と同様の意味のC<sub>1</sub>～C<sub>6</sub>アルキル基とスルルスルファモイル基とからなる基を意味し、その好適な具体例としては、N-メチルスルファモイル及びN,N-ジメチルスルファモイル等が挙げられる。

また、R<sup>4</sup>、R<sup>5</sup>、R<sup>6</sup>、及びR<sup>7</sup>として特に好ましいのは、ハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、C<sub>1</sub>～C<sub>6</sub>アルキル基、C<sub>1</sub>～C<sub>6</sub>アルコキシ基、C<sub>2</sub>～C<sub>7</sub>アルコキシカルボニル基、C<sub>1</sub>～C<sub>6</sub>アルキルスルホニル基、及びC<sub>1</sub>～C<sub>6</sub>N-アルキルスルファモイル基が挙げられる。

R<sup>4</sup>、R<sup>5</sup>、R<sup>6</sup>、及びR<sup>7</sup>の置換基としてのC<sub>1</sub>～C<sub>6</sub>アルキル基、C<sub>2</sub>～C<sub>6</sub>アルケニル基、C<sub>2</sub>～C<sub>6</sub>アルキニル基、C<sub>3</sub>～C<sub>5</sub>アルキレン基、C<sub>3</sub>～C<sub>8</sub>シクロアルキル基、C<sub>3</sub>～C<sub>8</sub>シクロアルケニル基、C<sub>1</sub>～C<sub>6</sub>アルコキシ基、C<sub>1</sub>～C<sub>6</sub>アルキルチオ基、モノ(C<sub>1</sub>～C<sub>6</sub>アルキル)アミノ基、ジ(C<sub>1</sub>～C<sub>6</sub>アルキル)アミノ基、C<sub>3</sub>～C<sub>7</sub>ラクタム基、C<sub>2</sub>～C<sub>7</sub>N-アルキルカルバモイル基、C<sub>4</sub>～C<sub>9</sub>N-シクロアルキルカルバモイル基、N-(C<sub>7</sub>～C<sub>12</sub>フェニルアルキル)カルバモイル基、

又は  $C_2 \sim C_7$  アルコキシカルボニル基は、 $R^1$  の置換基、それら置換基のさらなる置換基、或いは  $R^4$ 、 $R^5$ 、 $R^6$  及び  $R^7$  についてそれぞれ定義されたものと同様であり、それぞれ同じ例を好適な具体例として挙げることができる。

$R^4$ 、 $R^5$ 、 $R^6$  及び  $R^7$  の置換基としての「( $C_1 \sim C_6$  アルコキシ) ( $C_1 \sim C_6$  アルコキシ) 基」とは、 $C_1 \sim C_6$  アルコキシ基と  $C_1 \sim C_6$  アルコキシ基からなる基を意味し、その好適な具体例はメトキシメトキシ、メトキシエトキシ、及びエトキシエトキシ基等が挙げられる。

$R^4$ 、 $R^5$ 、 $R^6$  及び  $R^7$  の置換基としての「フェニル ( $C_1 \sim C_6$  アルコキシ) 基」とは、フェニル基と  $C_1 \sim C_6$  アルコキシ基からなる基を意味し、その好適な具体例は、ベンジルオキシ、フェニルエトキシ、及びフェニルプロポキシ基等が挙げられる。

$R^4$ 、 $R^5$ 、 $R^6$  及び  $R^7$  の置換基としての「( $C_2 \sim C_7$  アルカノイル) ピペリジル基」とは、 $C_2 \sim C_7$  アルカノイル基とピペリジル基からなる基を意味し、その好適な具体例は 1 - (アセチル) - 4 - ピペリジル基等を挙げられる。

本発明の  $R^8$  における  $C_1 \sim C_6$  アルキル基の置換基の数、及び  $R^8$  における  $C_1 \sim C_6$  アルキル基の置換基であるフェニル基の置換基の数は、化学的に可能と考え得る数であり、好ましくは 0 ~ 15 個、より好ましくは 0 ~ 10 個、さらにより好ましくは 0 ~ 7 個である。

$R^8$  としての  $C_1 \sim C_6$  アルキル基は、 $R^1$  の置換基について定義されたものと同様であり、同じ例を好適な具体例として挙げることができる。

$R^8$  における  $C_1 \sim C_6$  アルキル基の置換基としてのハロゲン原子、 $C_3 \sim C_8$  シクロアルキル基、 $C_1 \sim C_6$  アルコキシ基、 $C_1 \sim C_6$  アルキルチオ基、 $C_2 \sim C_7$  アルカノイル基、 $C_2 \sim C_7$  アルコキシカルボニル基、 $C_2 \sim C_7$  アルカノイルオキシ基、 $C_2 \sim C_7$  アルカノイルアミノ基、 $C$

$_2 \sim C_7$  N-アルキルカルバモイル基、 $C_2 \sim C_6$  アルキルスルホニル基、モノ ( $C_1 \sim C_6$  アルキル) アミノ基及びジ ( $C_1 \sim C_6$  アルキル) アミノ基は、前記  $R^1$  の置換基について定義されたものと同様であり、それぞれ同じ例を好適な具体例として挙げることができる。

また、 $R^8$  における  $C_1 \sim C_6$  アルキル基の置換基としてのフェニル基の置換基である「ハロゲン原子」、「 $C_1 \sim C_6$  アルキル基」、又は「 $C_1 \sim C_6$  アルコキシ基」は、前記  $R^1$  の置換基について定義されたものと同様であり、それぞれ同じ例を好適な具体例として挙げることができる。

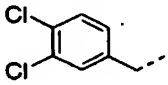
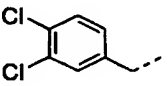
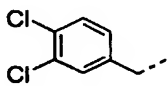
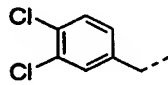
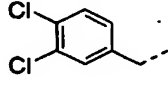
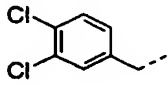
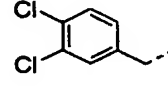
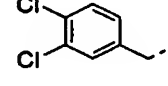
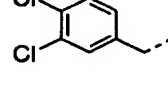
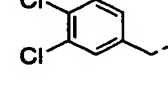
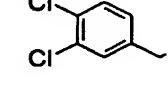
式 (I) のピペリジン誘導体の好適な具体例として、下記の表 1 ～ 表 8 に示される各置換基を含有する化合物を挙げることができる。なお、表 1 ～ 表 8 において、「compnd. No.」は「化合物番号」を意味する。

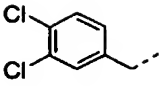
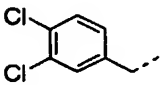
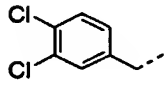
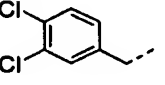
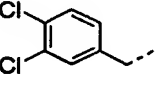
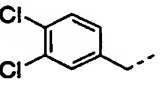
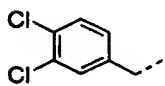
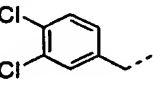
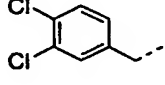
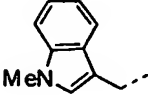
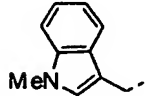
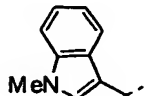
表 1 - 1 から表 1 - 6 は、 $X = \text{単結合}$ 、 $q = 0$ 、 $r = 0$ 、かつ  $Y = - (R^4) C = C (R^5) -$  で表される化合物の好適な具体例である。表 2 は、 $X = -CO-$ 、 $q = 0$ 、 $r = 0$ 、かつ  $Y = - (R^4) C = C (R^5) -$  で表される化合物の好適な具体例である。表 3 は、 $X = -SO_2-$ 、 $q = 0$ 、 $r = 0$ 、かつ  $Y = - (R^4) C = C (R^5) -$  で表される化合物の好適な具体例である。表 4 は、 $X = -CH_2-$ 、 $q = 0$ 、 $r = 0$ 、かつ  $Y = - (R^4) C = C (R^5) -$  で表される化合物の好適な具体例である。表 5 は、 $X = -CO-$ 、 $q = 0$ 、 $r = 0$ 、かつ  $Y = -S-$  で表される化合物の好適な具体例である。表 6 は、 $X = -CO-$ 、 $q = 0$ 、 $r = 0$ 、かつ  $Y = -N(R^8)-$  で表される化合物の好適な具体例である。表 7 は、 $X = -CO-$ 、 $q = 1$ 、 $r = 0$ 、かつ  $Y = - (R^4) C = C (R^5) -$  で表される化合物の好適な具体例である。表 8 は、 $X = -CS-$ 、 $q = 0$ 、 $r = 0$ 、かつ  $Y = - (R^4) C = C (R^5) -$

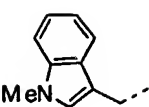
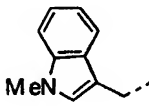
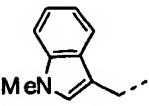
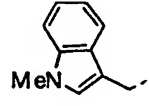
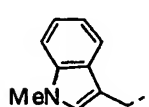
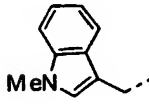
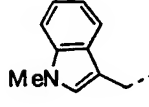
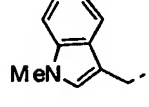
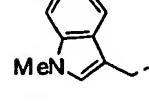
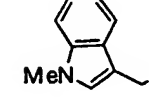
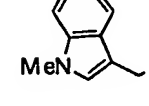
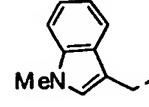


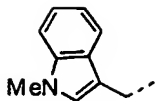
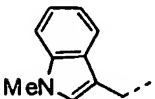
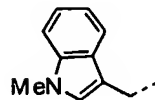
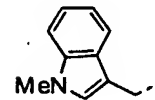
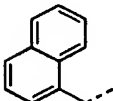
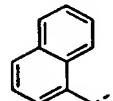
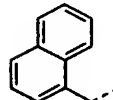
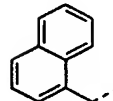
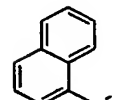
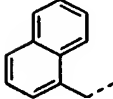
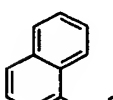
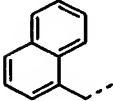
で表される化合物の好適な具体例である。

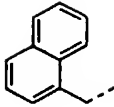
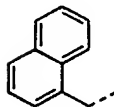
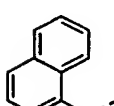
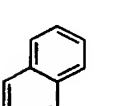
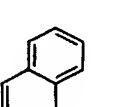
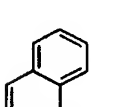
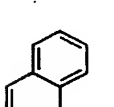
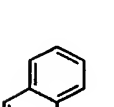
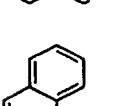
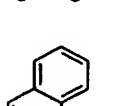
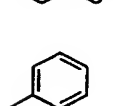
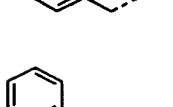
《表1-1》 X=単結合, q = 0, r = 0, Y = -(R4)C=C(R5)-

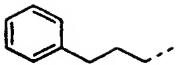
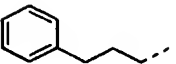
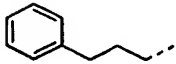
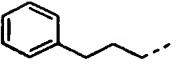
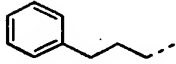
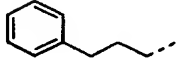
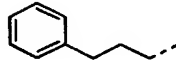
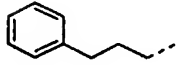
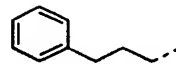
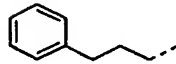
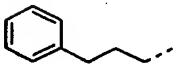
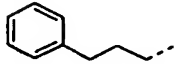
compnd NO.	R1	R2	R3	R4	R5	R6	R7
1-1-1		H	H	H	H	H	H
1-1-2		H	H	H	H	NO2	H
1-1-3		H	H	H	H	Me	H
1-1-4		H	H	H	H	Cl	H
1-1-5		H	H	H	H	F	H
1-1-6		H	H	H	H	CF3	H
1-1-7		H	H	H	H	COOH	H
1-1-8		H	H	H	Cl	Cl	H
1-1-9		H	H	H	H	H	Me
1-1-10		H	H	H	H	MeO	H
1-1-11		H	H	H	H	H	NO2

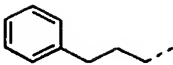
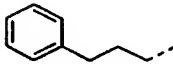
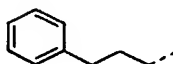
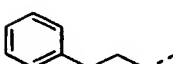
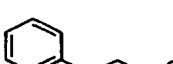
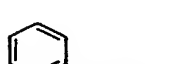
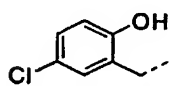
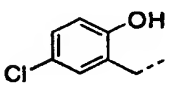
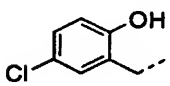
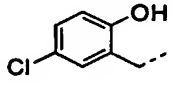
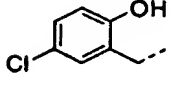
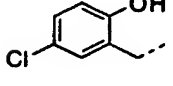
1-1-12		H	H	H	H	H	MeO
1-1-13		H	H	H	H	H	F
1-1-14		H	H	H	H	H	Cl
1-1-15		H	H	H	H	OCF3	H
1-1-16		H	H	H	H	CN	H
1-1-17		H	H	H	H	H	CN
1-1-18		H	H	H	H	H	COOH
1-1-19		H	H	H	H	OH	H
1-1-20		H	H	H	H	H	OH
1-1-21		H	H	H	H	NO2	H
1-1-22		H	H	H	H	Me	H
1-1-23		H	H	H	H	Cl	H

1-1-24		H	H	H	H	F	H
1-1-25		H	H	H	H	CF3	H
1-1-26		H	H	H	H	COOH	H
1-1-27		H	H	H	Cl	Cl	H
1-1-28		H	H	H	H	H	Me
1-1-29		H	H	H	H	MeO	H
1-1-30		H	H	H	H	H	NO2
1-1-31		H	H	H	H	H	MeO
1-1-32		H	H	H	H	H	F
1-1-33		H	H	H	H	H	Cl
1-1-34		H	H	H	H	OCF3	H
1-1-35		H	H	H	H	CN	H

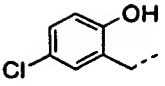
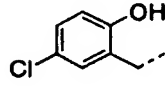
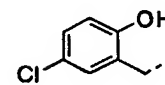
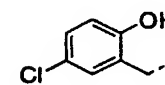
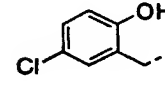
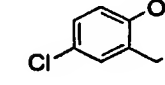
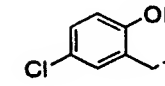
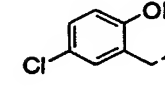
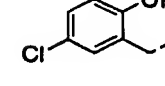
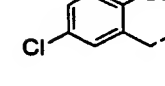
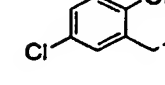
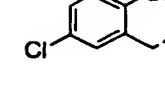
1-1-36		H	H	H	H	H	CN
1-1-37		H	H	H	H	H	COOH
1-1-38		H	H	H	H	OH	H
1-1-39		H	H	H	H	H	OH
1-1-40		H	H	H	H	NO2	H
1-1-41		H	H	H	H	Me	H
1-1-42		H	H	H	H	Cl	H
1-1-43		H	H	H	H	F	H
1-1-44		H	H	H	H	CF3	H
1-1-45		H	H	H	H	COOH	H
1-1-46		H	H	H	Cl	Cl	H
1-1-47		H	H	H	H	H	Me

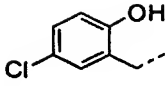
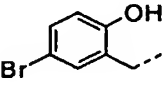
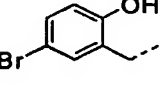
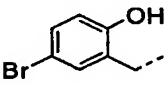
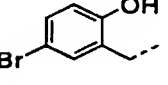
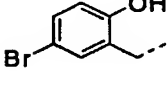
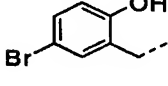
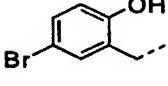
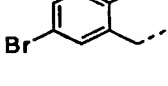
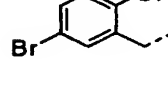
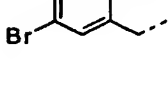
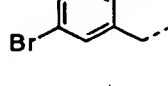
1-1-48		H	H	H	H	MeO	H
1-1-49		H	H	H	H	H	NO2
1-1-50		H	H	H	H	H	MeO
1-1-51		H	H	H	H	H	F
1-1-52		H	H	H	H	H	Cl
1-1-53		H	H	H	H	OCF3	H
1-1-54		H	H	H	H	CN	H
1-1-55		H	H	H	H	H	CN
1-1-56		H	H	H	H	H	COOH
1-1-57		H	H	H	H	OH	H
1-1-58		H	H	H	H	H	OH
1-1-59		H	H	H	H	NO2	H

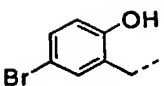
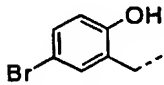
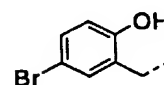
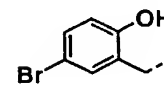
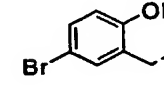
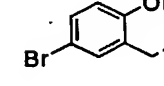
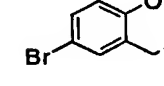
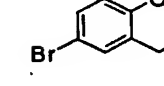
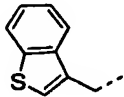
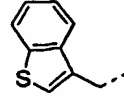
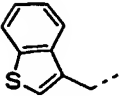
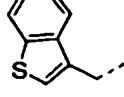
1-1-60		H	H	H	H	Me	H
1-1-61		H	H	H	H	Cl	H
1-1-62		H	H	H	H	F	H
1-1-63		H	H	H	H	CF3	H
1-1-64		H	H	H	H	COOH	H
1-1-65		H	H	H	Cl	Cl	H
1-1-66		H	H	H	H	H	Me
1-1-67		H	H	H	H	MeO	H
1-1-68		H	H	H	H	H	NO2
1-1-69		H	H	H	H	H	MeO
1-1-70		H	H	H	H	H	F
1-1-71		H	H	H	H	H	Cl

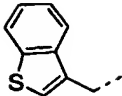
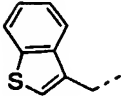
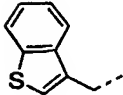
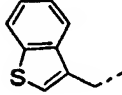
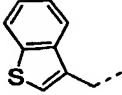
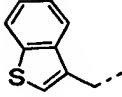
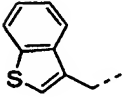
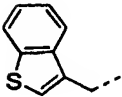
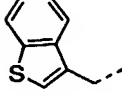
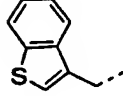
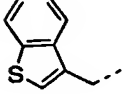
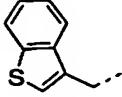
1-1-72		H	H	H	H	OCF <sub>3</sub>	H
1-1-73		H	H	H	H	CN	H
1-1-74		H	H	H	H	H	CN
1-1-75		H	H	H	H	H	COOH
1-1-76		H	H	H	H	OH	H
1-1-77		H	H	H	H	H	OH
1-1-78		H	H	H	H	NO <sub>2</sub>	H
1-1-79		H	H	H	H	Me	H
1-1-80		H	H	H	H	Cl	H
1-1-81		H	H	H	H	F	H
1-1-82		H	H	H	H	CF <sub>3</sub>	H
1-1-83		H	H	H	H	COOH	H

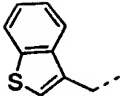
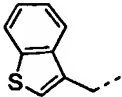
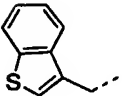
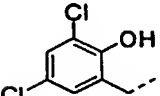
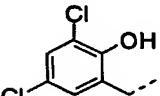
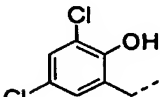
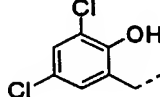
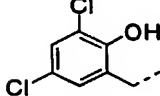
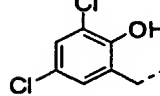
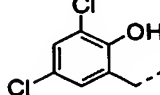
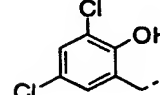
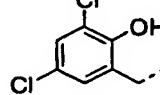


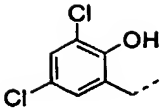
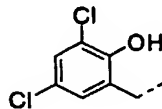
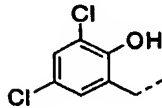
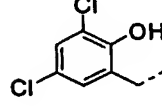
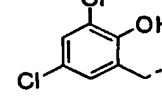
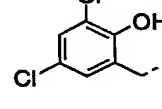
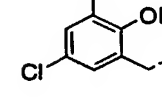
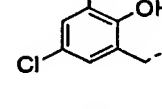
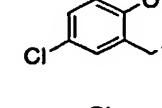
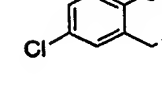
1-1-84		H	H	H	Cl	Cl	H
1-1-85		H	H	H	H	H	Me
1-1-86		H	H	H	H	MeO	H
1-1-87		H	H	H	H	H	NO2
1-1-88		H	H	H	H	H	MeO
1-1-89		H	H	H	H	H	F
1-1-90		H	H	H	H	H	Cl
1-1-91		H	H	H	H	OCF3	H
1-1-92		H	H	H	H	CN	H
1-1-93		H	H	H	H	H	CN
1-1-94		H	H	H	H	H	COOH
1-1-95		H	H	H	H	OH	H

1-1-96		H	H	H	H	H	OH
1-1-97		H	H	H	H	NO2	H
1-1-98		H	H	H	H	Me	H
1-1-99		H	H	H	H	Cl	H
1-1-100		H	H	H	H	F	H
1-1-101		H	H	H	H	CF3	H
1-1-102		H	H	H	H	COOH	H
1-1-103		H	H	H	Cl	Cl	H
1-1-104		H	H	H	H	H	Me
1-1-105		H	H	H	H	MeO	H
1-1-106		H	H	H	H	H	NO2
1-1-107		H	H	H	H	H	MeO

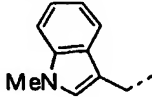
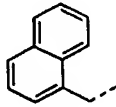
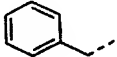
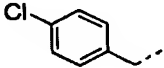
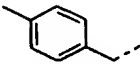
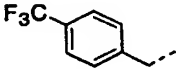
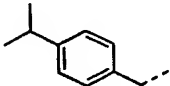
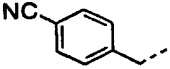
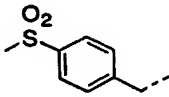
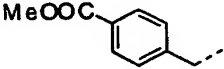
1-1-108		H	H	H	H	H	F
1-1-109		H	H	H	H	H	Cl
1-1-110		H	H	H	H	OCF3	H
1-1-111		H	H	H	H	CN	H
1-1-112		H	H	H	H	H	CN
1-1-113		H	H	H	H	H	COOH
1-1-114		H	H	H	H	OH	H
1-1-115		H	H	H	H	H	OH
1-1-116		H	H	H	H	NO2	H
1-1-117		H	H	H	H	Me	H
1-1-118		H	H	H	H	Cl	H
1-1-119		H	H	H	H	F	H

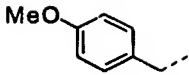
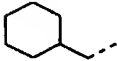
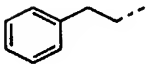
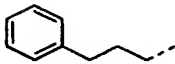
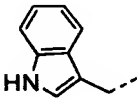
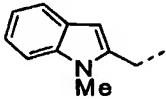
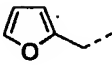
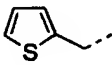
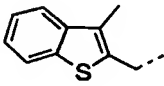
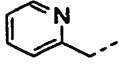
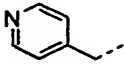
1-1-120		H	H	H	H	CF3	H
1-1-121		H	H	H	H	COOH	H
1-1-122		H	H	H	Cl	Cl	H
1-1-123		H	H	H	H	H	Me
1-1-124		H	H	H	H	MeO	H
1-1-125		H	H	H	H	H	NO2
1-1-126		H	H	H	H	H	MeO
1-1-127		H	H	H	H	H	F
1-1-128		H	H	H	H	H	Cl
1-1-129		H	H	H	H	OCF3	H
1-1-130		H	H	H	H	CN	H
1-1-131		H	H	H	H	H	CN

1-1-132		H	H	H	H	H	COOH
1-1-133		H	H	H	H	OH	H
1-1-134		H	H	H	H	H	OH
1-1-135		H	H	H	H	NO2	H
1-1-136		H	H	H	H	Me	H
1-1-137		H	H	H	H	Cl	H
1-1-138		H	H	H	H	F	H
1-1-139		H	H	H	H	CF3	H
1-1-140		H	H	H	H	COOH	H
1-1-141		H	H	H	Cl	Cl	H
1-1-142		H	H	H	H	H	Me
1-1-143		H	H	H	H	MeO	H

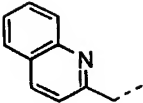
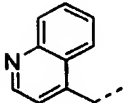
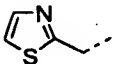
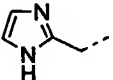
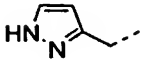
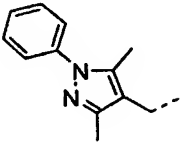
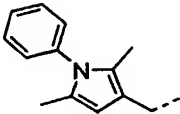
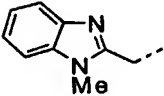
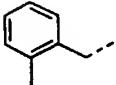
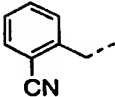
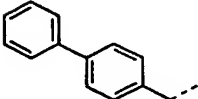
1-1-144		H	H	H	H	H	NO <sub>2</sub>
1-1-145		H	H	H	H	H	MeO
1-1-146		H	H	H	H	H	F
1-1-147		H	H	H	H	H	Cl
1-1-148		H	H	H	H	OCF <sub>3</sub>	H
1-1-149		H	H	H	H	CN	H
1-1-150		H	H	H	H	H	CN
1-1-151		H	H	H	H	H	COOH
1-1-152		H	H	H	H	OH	H
1-1-153		H	H	H	H	H	OH

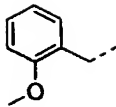
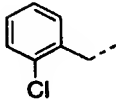
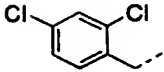
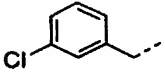
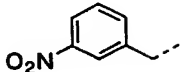
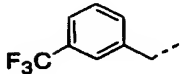
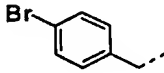
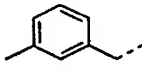
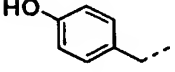
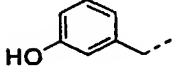
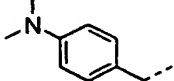
《表1-2》 X = 単結合, q = 0, r = 0, Y = -(R4)C=C(R5)-

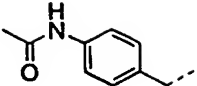
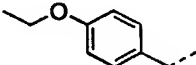
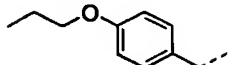
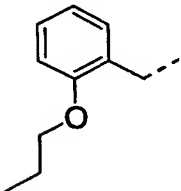
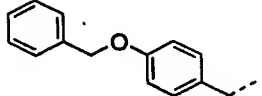
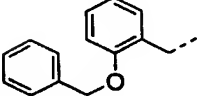
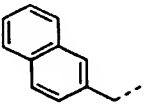
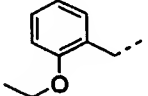
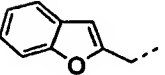
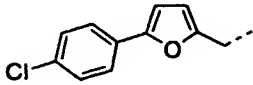
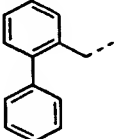
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1-2-3		H	H	H	H	H	H
1-2-4		H	H	H	H	H	H
1-2-5		H	H	H	H	H	H
1-2-6		H	H	H	H	H	H
1-2-7		H	H	H	H	H	H
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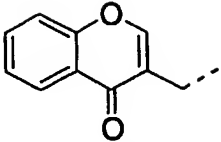
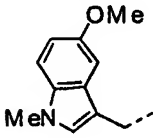
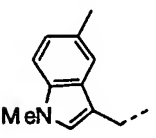
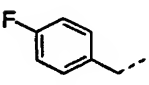
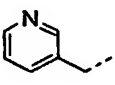
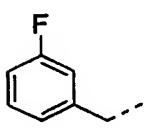
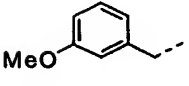
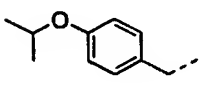
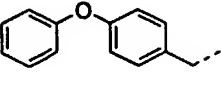
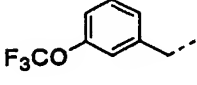
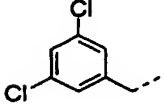
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1-2-13		H	H	H	H	H	H
1-2-14		H	H	H	H	H	H
1-2-15		H	H	H	H	H	H
1-2-16		H	H	H	H	H	H
1-2-17		H	H	H	H	H	H
1-2-18		H	H	H	H	H	H
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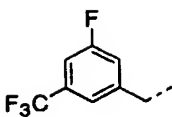
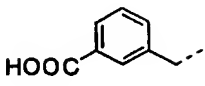
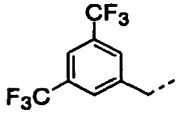
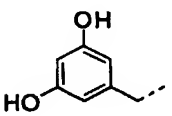
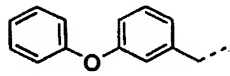
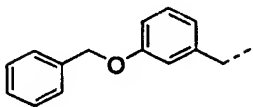
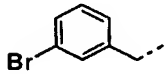
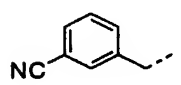
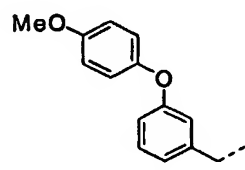
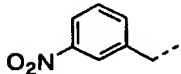
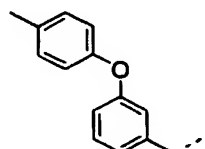


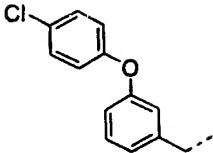
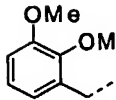
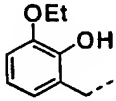
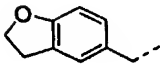
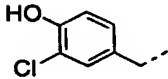
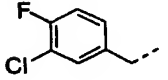
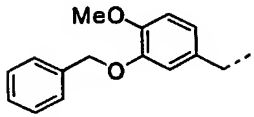
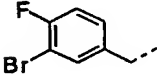
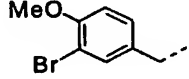
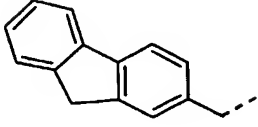
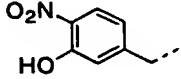
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1-2-24		H	H	H	H	H	H
1-2-25		H	H	H	H	H	H
1-2-26		H	H	H	H	H	H
1-2-27		H	H	H	H	H	H
1-2-28		H	H	H	H	H	H
1-2-29		H	H	H	H	H	H
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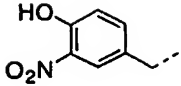
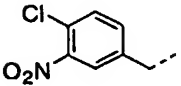
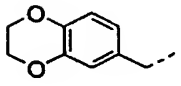
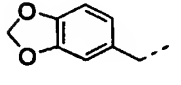
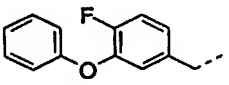
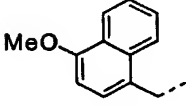
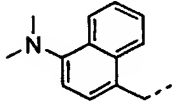
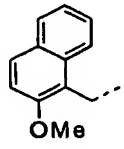
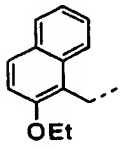
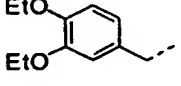
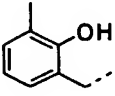
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1-2-37		H	H	H	H	H	H
1-2-38		H	H	H	H	H	H
1-2-39		H	H	H	H	H	H
1-2-40		H	H	H	H	H	H
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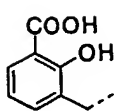
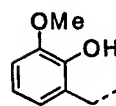
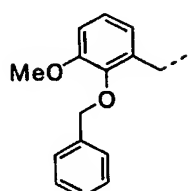
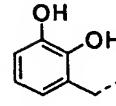
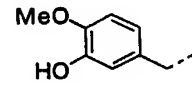
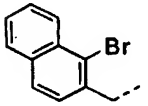
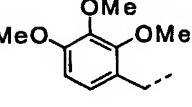
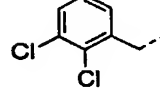
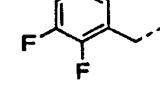
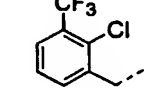
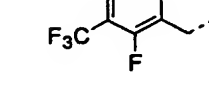
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1-2-48		H	H	H	H	H	H
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1-2-51		H	H	H	H	H	H
1-2-52		H	H	H	H	H	H
1-2-53		H	H	H	H	H	H
1-2-54		H	H	H	H	H	H

1-2-55		H	H	H	H	H	H
1-2-56		H	H	H	H	H	H
1-2-57		H	H	H	H	H	H
1-2-58		H	H	H	H	H	H
1-2-59		H	H	H	H	H	H
1-2-60		H	H	H	H	H	H
1-2-61		H	H	H	H	H	H
1-2-62		H	H	H	H	H	H
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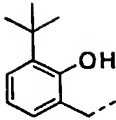
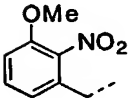
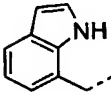
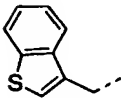
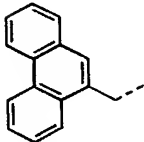
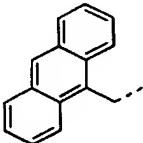
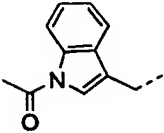
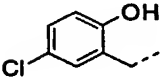
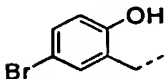
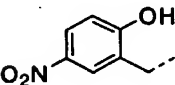
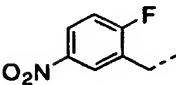
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1-2-67		H	H	H	H	H	H
1-2-68		H	H	H	H	H	H
1-2-69		H	H	H	H	H	H
1-2-70		H	H	H	H	H	H
1-2-71		H	H	H	H	H	H
1-2-72		H	H	H	H	H	H
1-2-73		H	H	H	H	H	H
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1-2-76		H	H	H	H	H	H

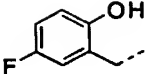
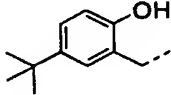
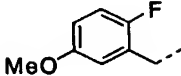
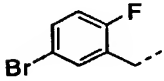
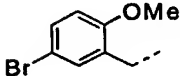
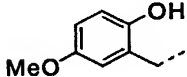
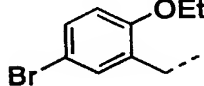
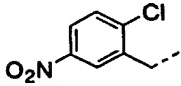
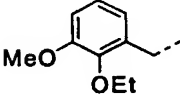
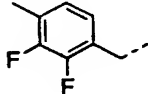
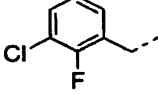
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1-2-80		H	H	H	H	H	H
1-2-81		H	H	H	H	H	H
1-2-82		H	H	H	H	H	H
1-2-83		H	H	H	H	H	H
1-2-84		H	H	H	H	H	H
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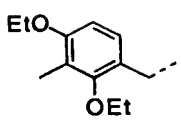
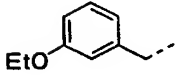
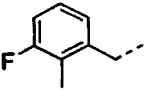
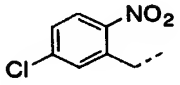
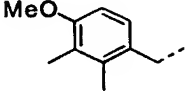
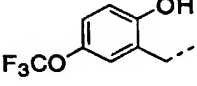
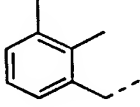
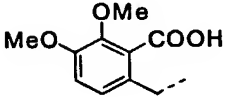
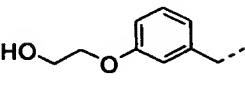
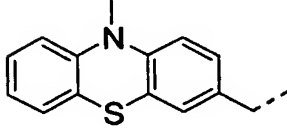
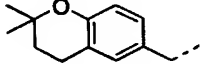
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1-2-92		H	H	H	H	H	H
1-2-93		H	H	H	H	H	H
1-2-94		H	H	H	H	H	H
1-2-95		H	H	H	H	H	H
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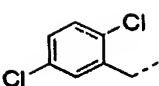
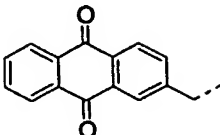
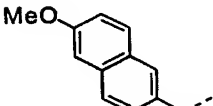
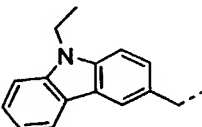
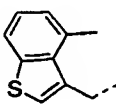
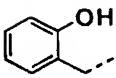
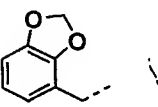
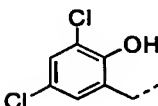
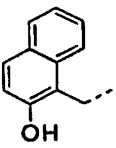
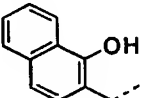
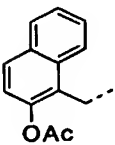
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1-2-102		H	H	H	H	H	H
1-2-103		H	H	H	H	H	H
1-2-104		H	H	H	H	H	H
1-2-105		H	H	H	H	H	H
1-2-106		H	H	H	H	H	H
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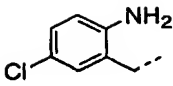
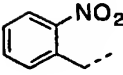
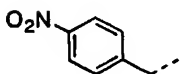
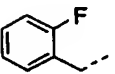
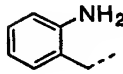
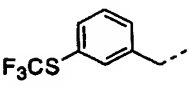
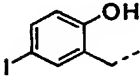
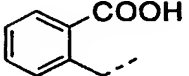
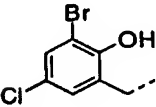
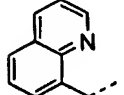
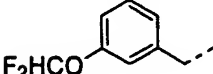


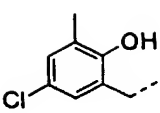
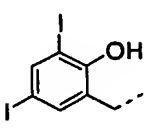
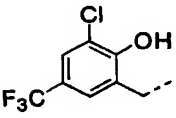
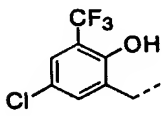
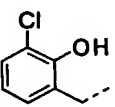
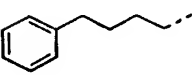
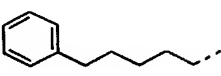
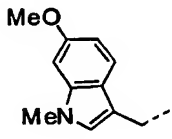
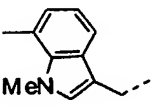
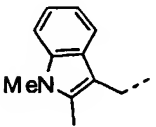
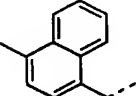
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1-2-112		H	H	H	H	H	H
1-2-113		H	H	H	H	H	H
1-2-114		H	H	H	H	H	H
1-2-115		H	H	H	H	H	H
1-2-116		H	H	H	H	H	H
1-2-117		H	H	H	H	H	H
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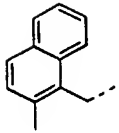
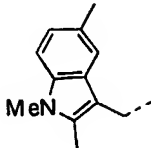
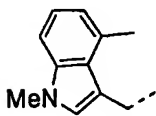
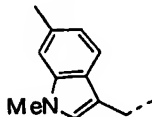
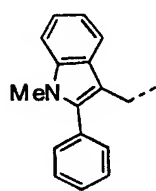
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1-2-124		H	H	H	H	H	H
1-2-125		H	H	H	H	H	H
1-2-126		H	H	H	H	H	H
1-2-127		H	H	H	H	H	H
1-2-128		H	H	H	H	H	H
1-2-129		H	H	H	H	H	H
1-2-130		H	H	H	H	H	H
1-2-131		H	H	H	H	H	H

1-2-132		H	H	H	H	H	H
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1-2-134		H	H	H	H	H	H
1-2-135		H	H	H	H	H	H
1-2-136		H	H	H	H	H	H
1-2-137		H	H	H	H	H	H
1-2-138		H	H	H	H	H	H
1-2-139		H	H	H	H	H	H
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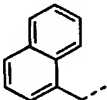
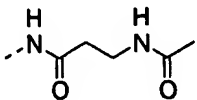
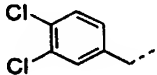
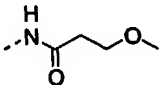
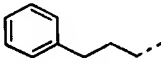
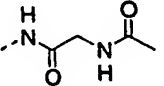
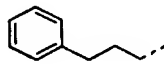
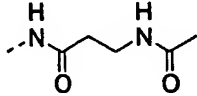
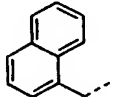
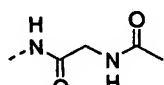
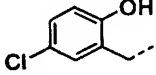
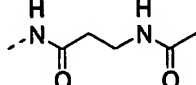
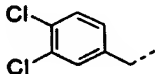
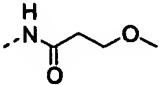
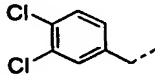
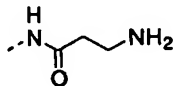
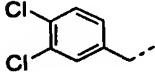
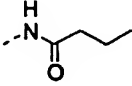
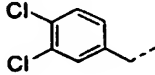
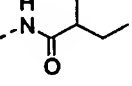
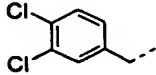
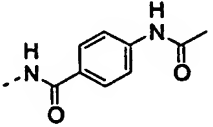
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1-2-145		H	H	H	H	H	H
1-2-146		H	H	H	H	H	H
1-2-147		H	H	H	H	H	H
1-2-148		H	H	H	H	H	H
1-2-149		H	H	H	H	H	H
1-2-150		H	H	H	H	H	H
1-2-151		H	H	H	H	H	H
1-2-152		H	H	H	H	H	H
1-2-153		H	H	H	H	H	H

1-2-154		H	H	H	H	H	H
1-2-155		H	H	H	H	H	H
1-2-156		H	H	H	H	H	H
1-2-157		H	H	H	H	H	H
1-2-158		H	H	H	H	H	H
1-2-159		H	H	H	H	H	H
1-2-160		H	H	H	H	H	H
1-2-161		H	H	H	H	H	H
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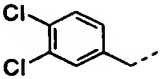
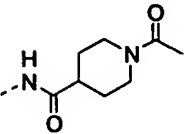
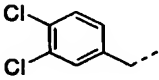
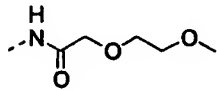
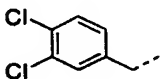
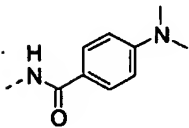
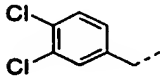
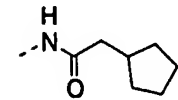
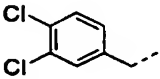
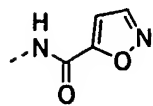
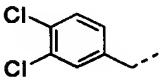
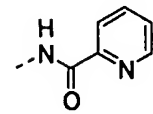
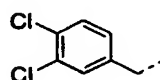
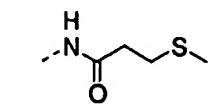
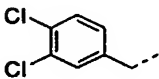
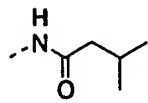
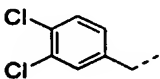
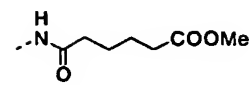
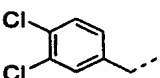
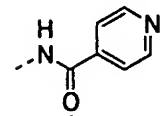
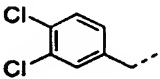
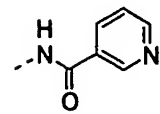
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1-2-167		H	H	H	H	H	H
1-2-168		H	H	H	H	H	H
1-2-169		H	H	H	H	H	H
1-2-170		H	H	H	H	H	H
1-2-171		H	H	H	H	H	H
1-2-172		H	H	H	H	H	H
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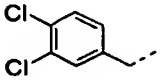
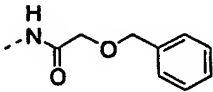
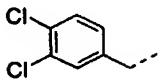
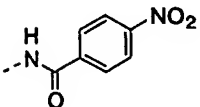
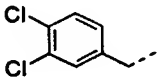
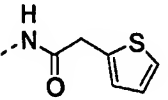
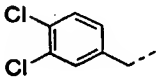
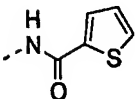
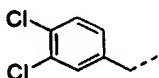
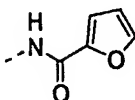
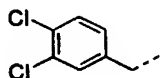
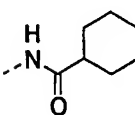
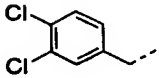
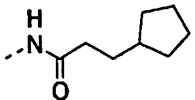
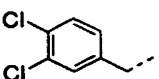
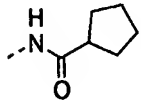
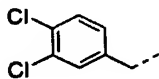
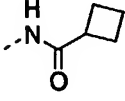
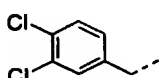
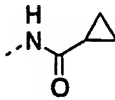
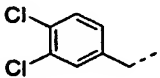
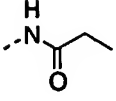
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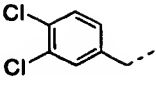
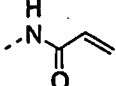
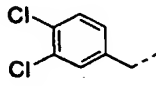
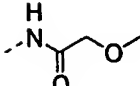
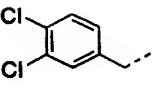
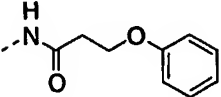
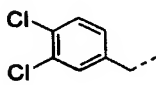
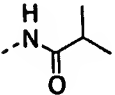
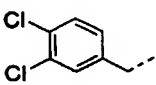
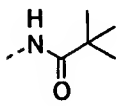
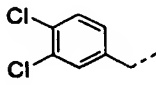
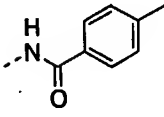
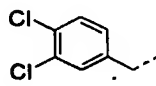
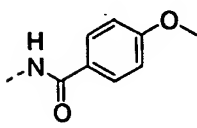
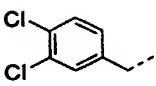
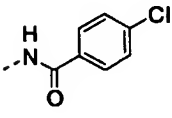
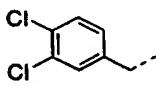
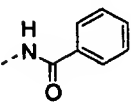
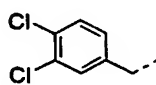

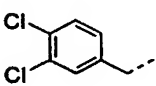
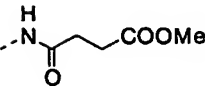
《表1-3》 X = 単結合, q = 0, r = 0, Y = -(R4)C=C(R5)-

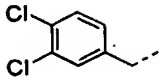
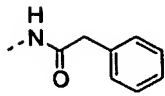
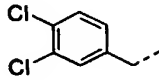
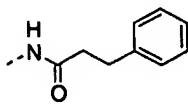
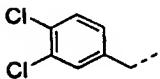
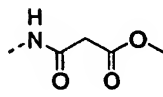
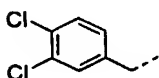
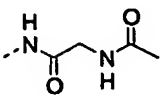
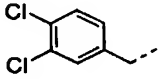
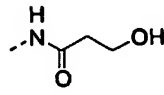
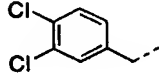
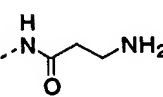
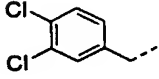
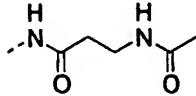
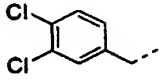
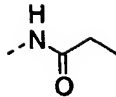
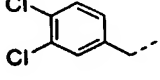
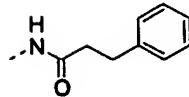
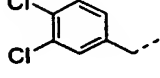
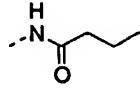
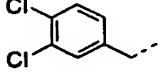
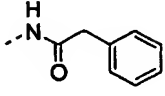
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1-3-3		H	H	H	H	H	
1-3-4		H	H	H	H	H	
1-3-5		H	H	H	H	H	
1-3-6		H	H	H	H	H	
1-3-7		H	H	H	H		H
1-3-8		H	H	H	H		H
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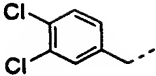
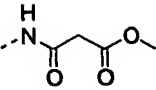
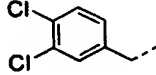
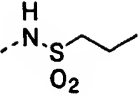
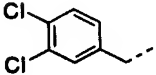
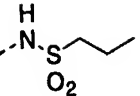
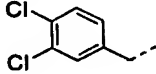
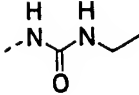
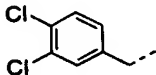
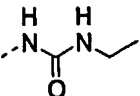
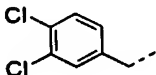
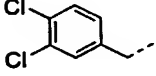
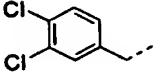
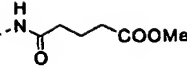
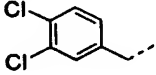
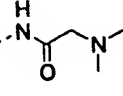
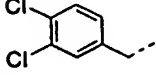
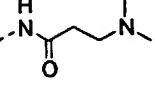
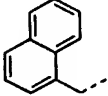
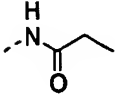


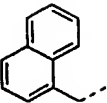
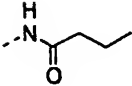
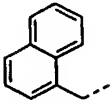
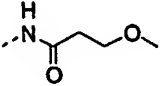
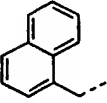
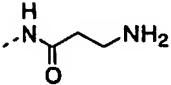
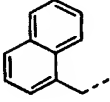
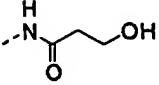
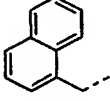
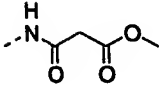
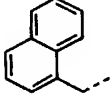
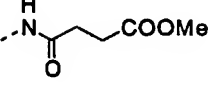
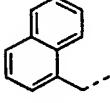
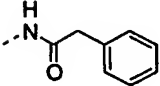
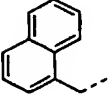
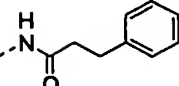
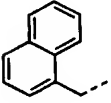
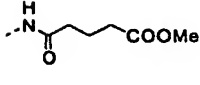
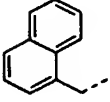
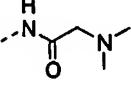
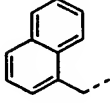
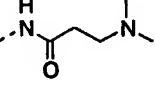
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1-3-17		H	H	H	H	H	
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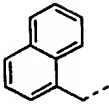
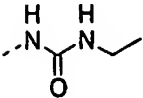
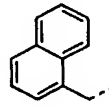
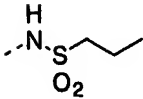
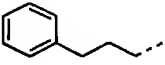
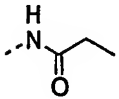
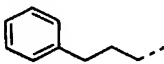
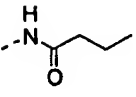
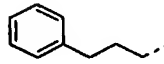
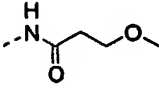
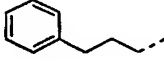
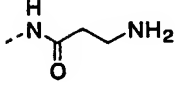
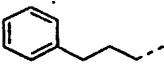
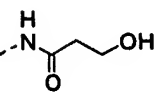
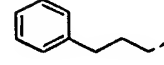
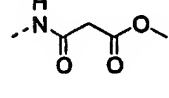
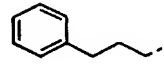
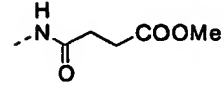
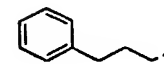
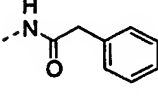
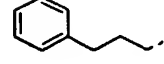
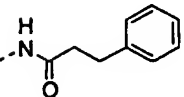
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1-3-27		H	H	H	H	H	
1-3-28		H	H	H	H	H	
1-3-29		H	H	H	H	H	
1-3-30		H	H	H	H	H	
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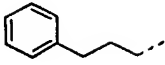
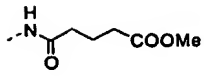
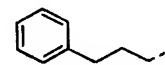
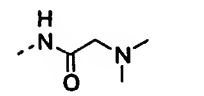
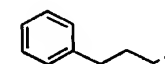
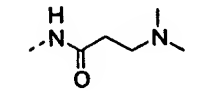
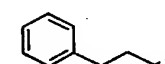
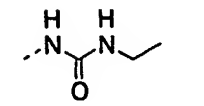
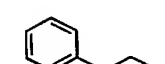
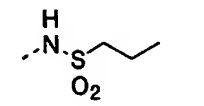
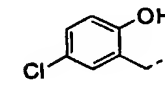
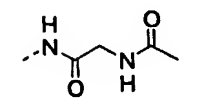
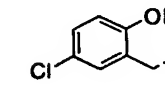
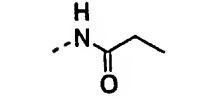
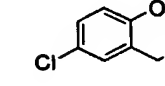
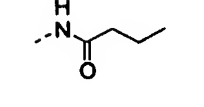
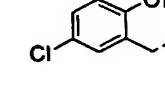
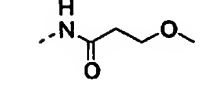
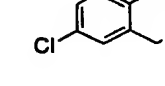
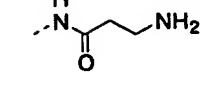
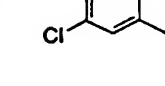
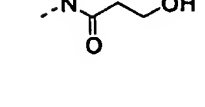
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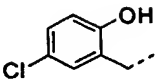
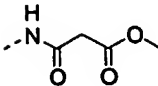
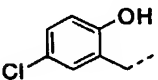
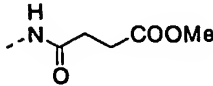
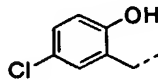
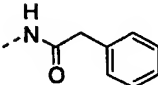
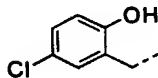
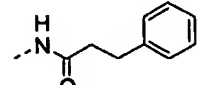
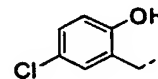
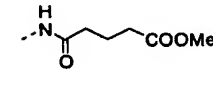
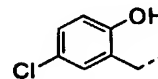
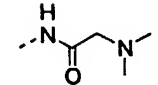
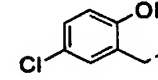
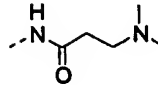
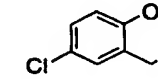
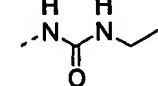
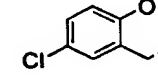
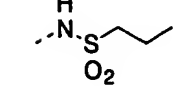
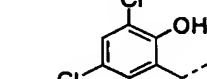
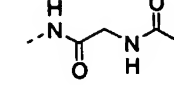
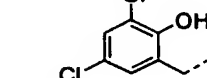
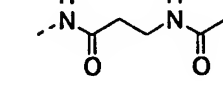
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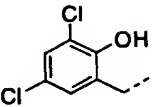
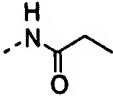
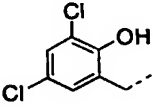
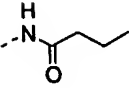
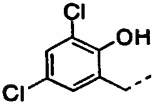
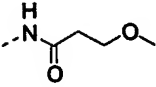
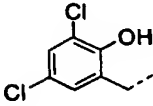
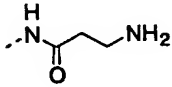
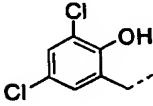
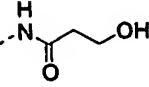
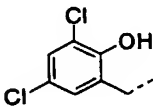
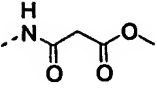
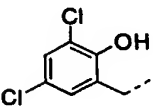
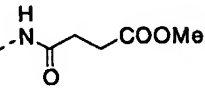
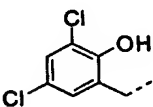
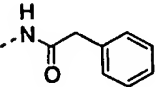
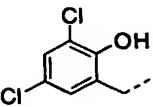
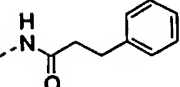
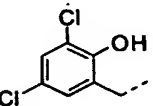
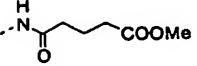
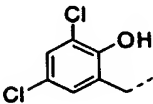
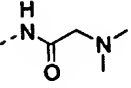
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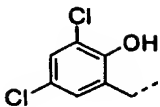
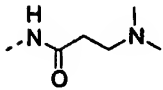
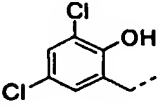
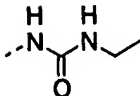
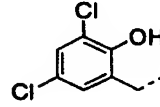
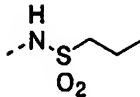
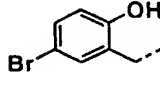
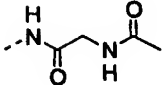
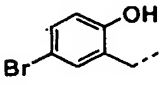
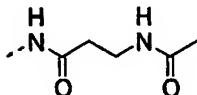
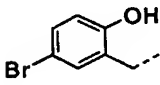
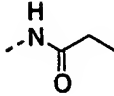
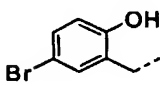
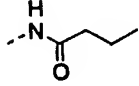
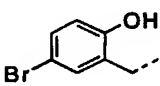
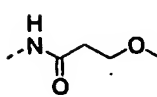
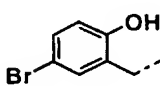
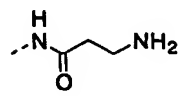
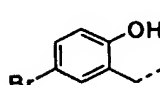
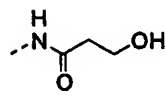
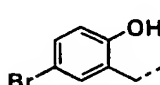
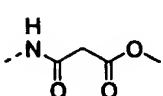
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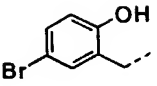
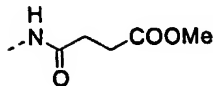
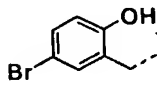
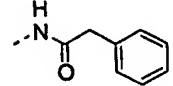
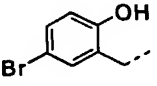
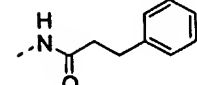
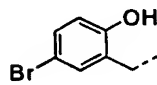
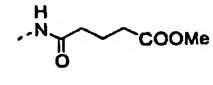
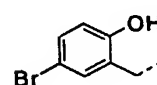
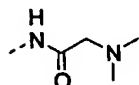
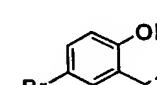
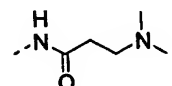
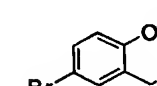
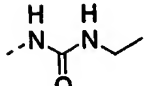
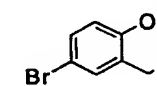
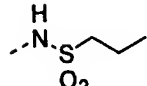
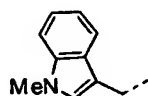
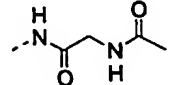
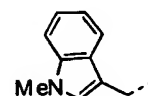
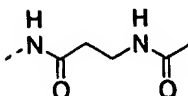
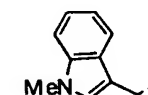
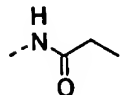
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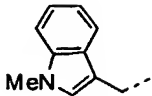
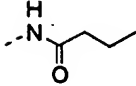
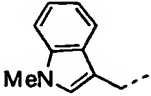
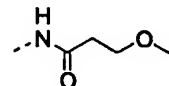
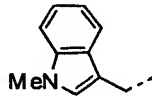
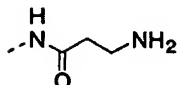
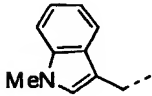
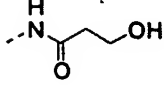
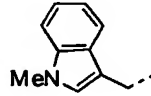
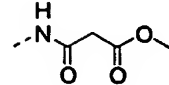
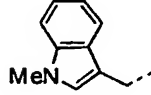
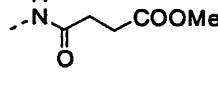
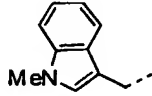
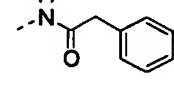
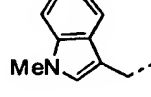
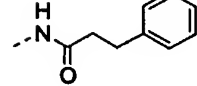
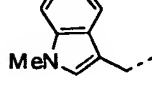
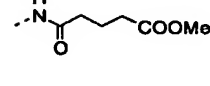
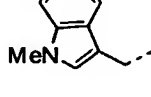
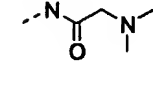
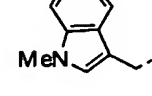
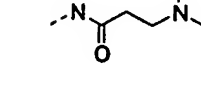


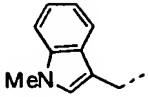
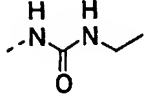
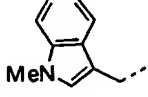
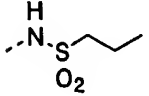
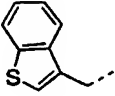
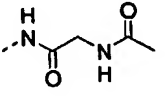
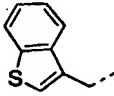
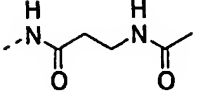
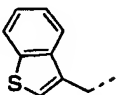
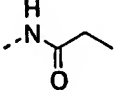
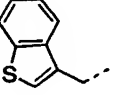
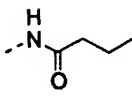
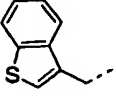
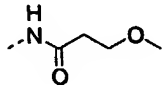
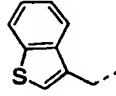
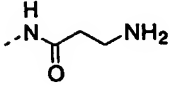
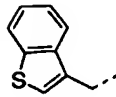
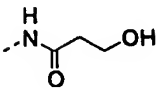
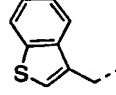
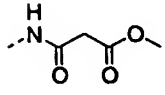
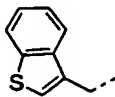
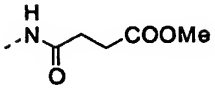
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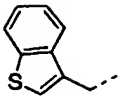
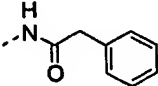
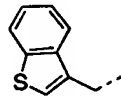
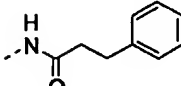
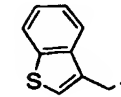
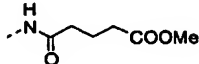
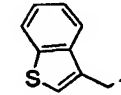
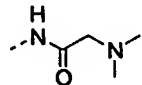
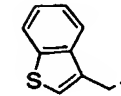
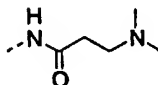
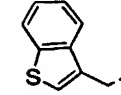
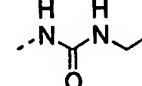
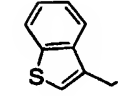
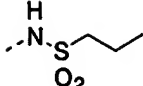
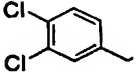
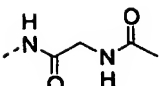
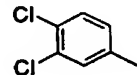
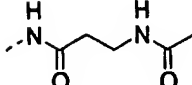
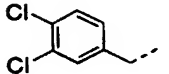
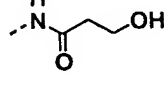
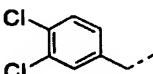
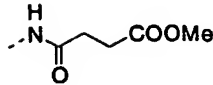
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1-3-117		H	H	H	H	H	
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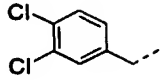
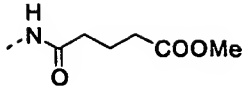
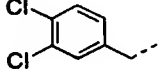
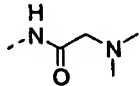
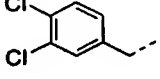
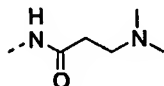
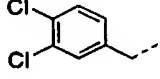
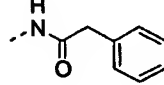
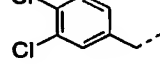
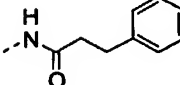
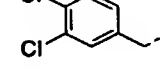
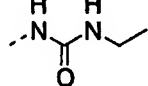
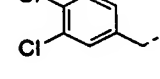
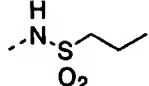
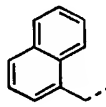
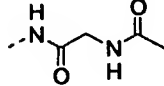
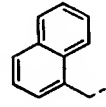
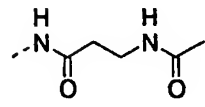
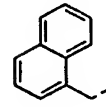
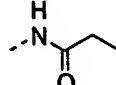
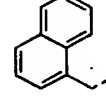
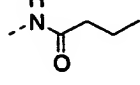
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1-3-126		H	H	H	H	H	
1-3-127		H	H	H	H	H	
1-3-128		H	H	H	H	H	
1-3-129		H	H	H	H	H	
1-3-130		H	H	H	H	H	
1-3-131		H	H	H	H	H	
1-3-132		H	H	H	H	H	

1-3-133		H	H	H	H	H	
1-3-134		H	H	H	H	H	
1-3-135		H	H	H	H	H	
1-3-136		H	H	H	H	H	
1-3-137		H	H	H	H	H	
1-3-138		H	H	H	H	H	
1-3-139		H	H	H	H	H	
1-3-140		H	H	H	H	H	
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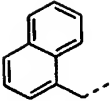
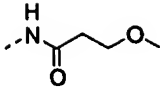
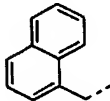
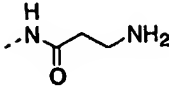
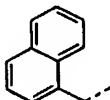
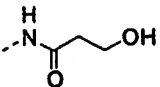
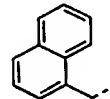
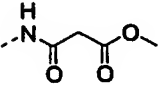
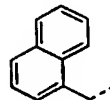
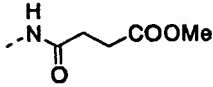
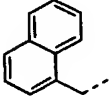
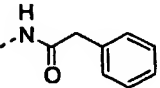
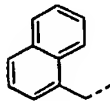
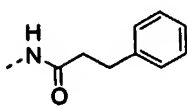
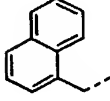
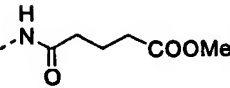
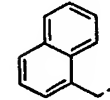
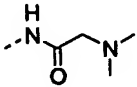
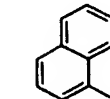
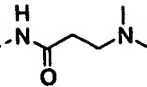
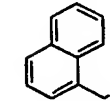
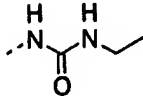
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1-3-150		H	H	H	H	H	
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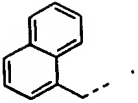
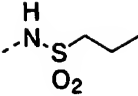
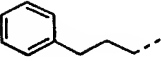
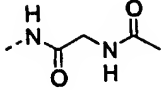
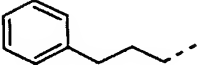
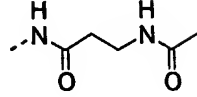
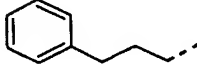
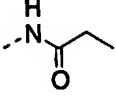
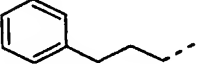
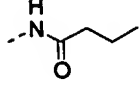
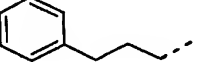
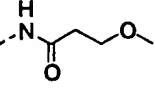
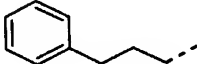
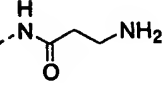
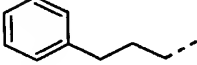
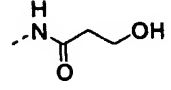
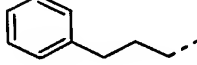
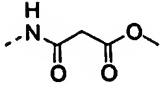
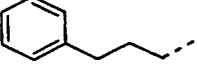
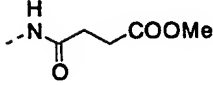
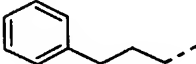
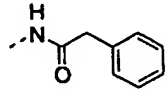
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1-3-159		H	H	H	H	H	
1-3-160		H	H	H	H	H	
1-3-161		H	H	H	H	H	
1-3-162		H	H	H	H	H	
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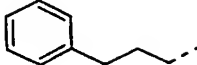
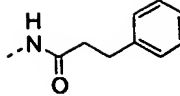
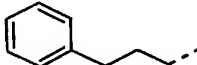
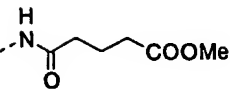
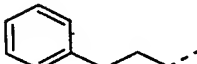
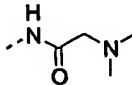
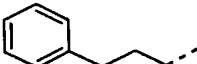
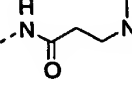
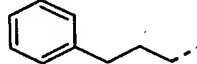
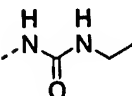
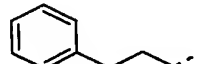
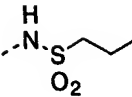
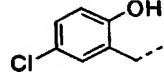
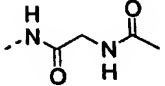
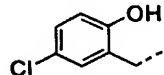
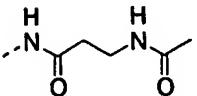
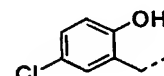
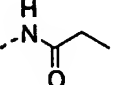
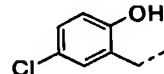
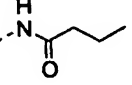
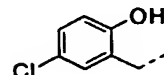
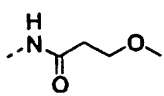
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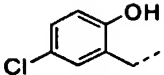
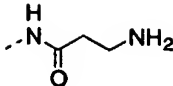
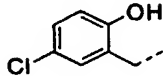
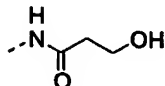
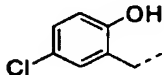
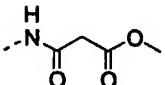
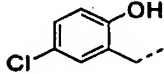
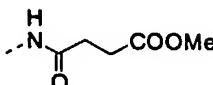
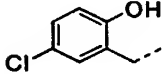
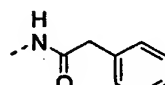
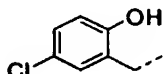
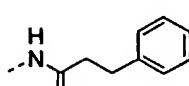
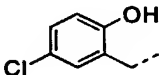
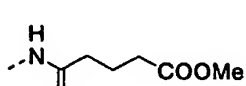
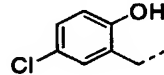
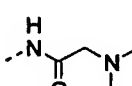
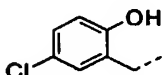
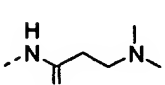
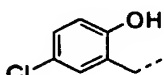
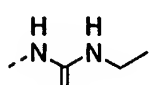
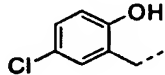
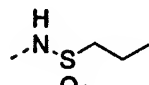
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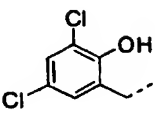
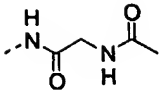
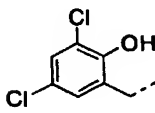
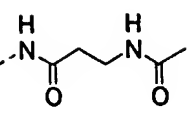
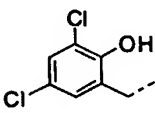
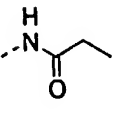
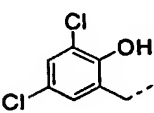
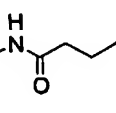
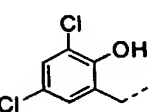
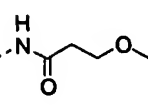
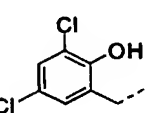
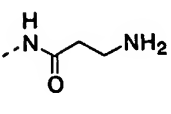
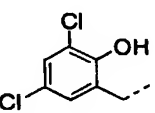
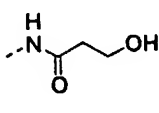
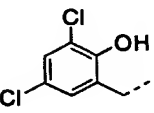
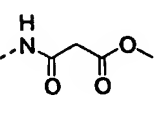
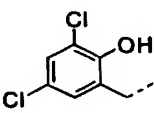
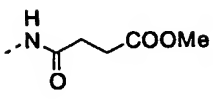
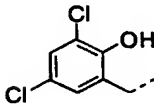
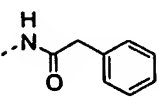
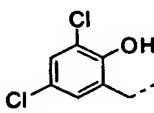
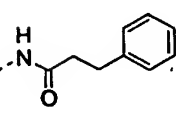


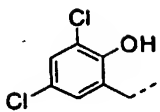
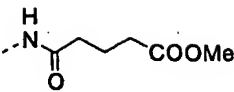
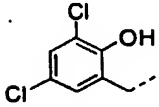
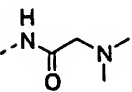
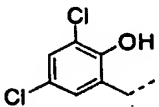
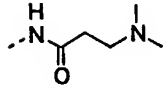
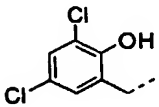
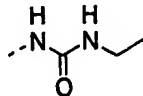
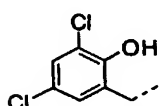
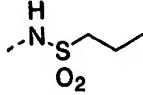
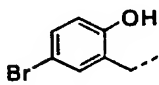
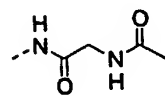
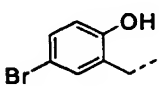
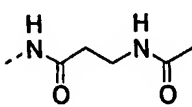
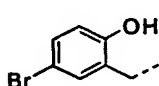
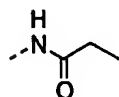
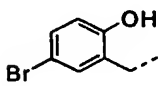
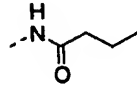
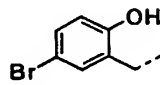
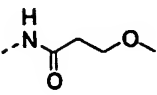
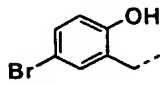
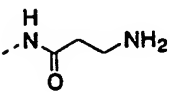
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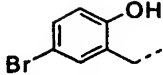
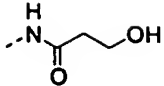
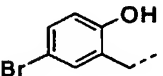
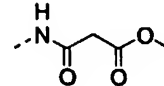
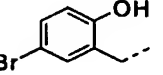
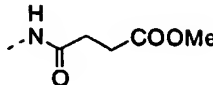
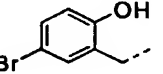
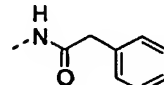
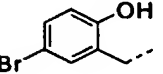
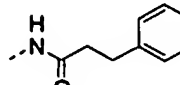
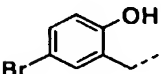
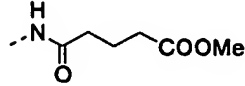
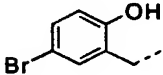
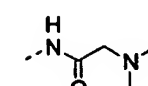
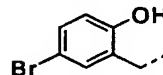
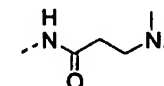
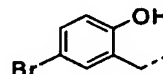
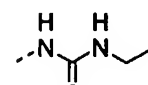
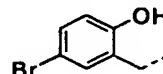
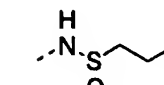
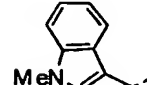
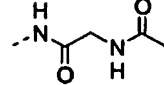
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1-3-204		H	H	H	H		H
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1-3-208		H	H	H	H		H
1-3-209		H	H	H	H		H

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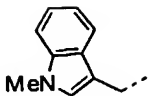
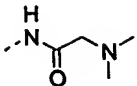
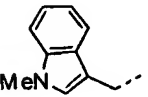
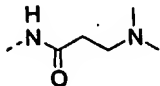
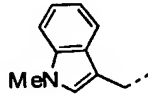
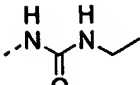
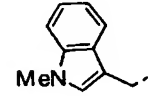
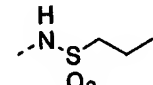
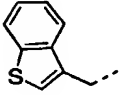
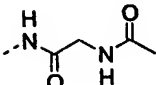
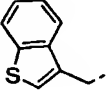
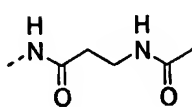
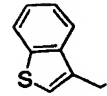
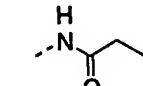
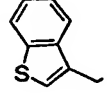
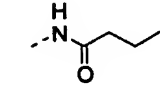
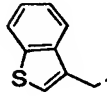
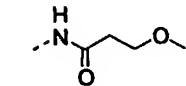
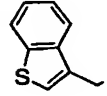
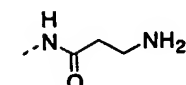
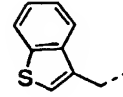
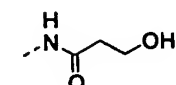
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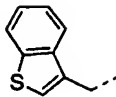
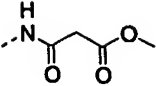
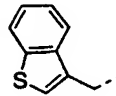
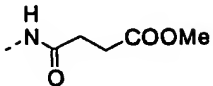
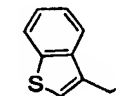
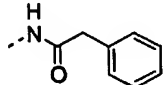
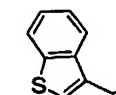
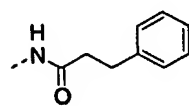
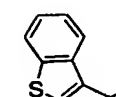
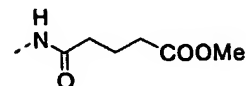
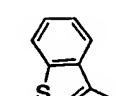
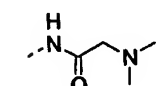
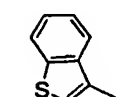
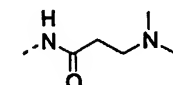
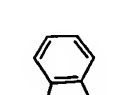
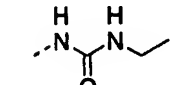
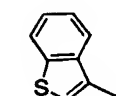
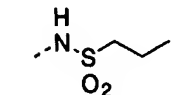
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1-3-253		H	H	H	H		H

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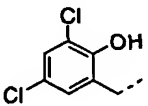
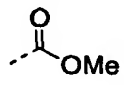
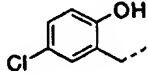
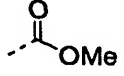
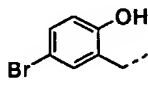
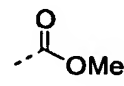
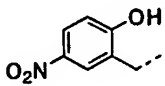
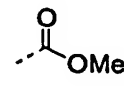
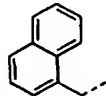
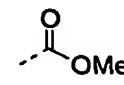
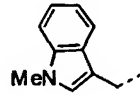
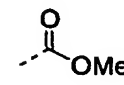
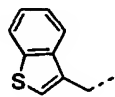
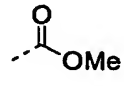
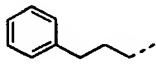
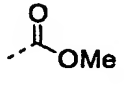
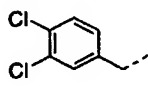
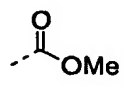
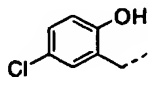
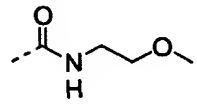
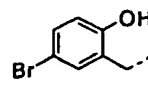
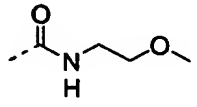
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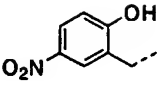
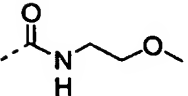
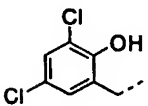
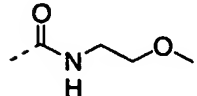
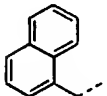
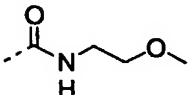
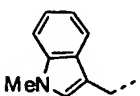
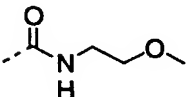
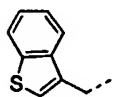
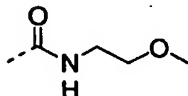
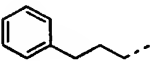
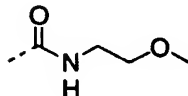
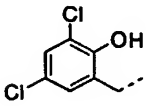
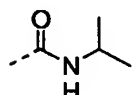
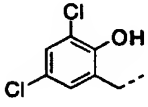

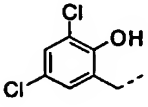
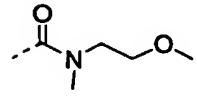
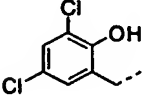
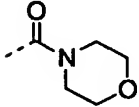
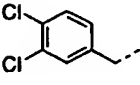
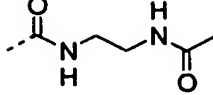
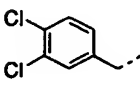
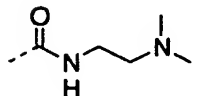


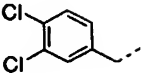
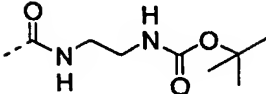
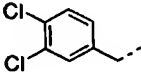
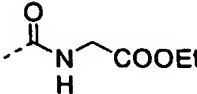
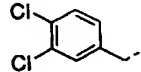
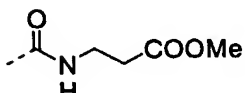
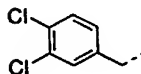
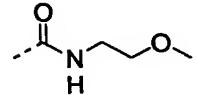
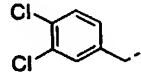
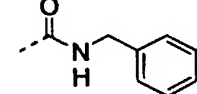
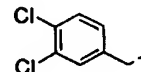
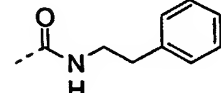
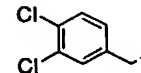
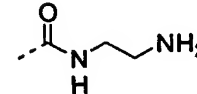

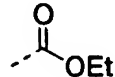

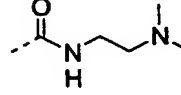

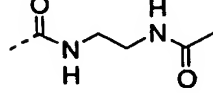

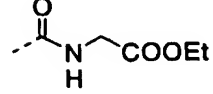

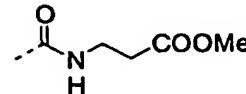
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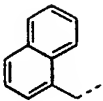
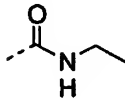
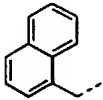
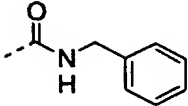
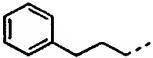
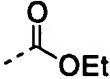
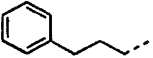
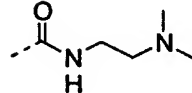
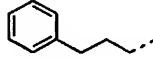
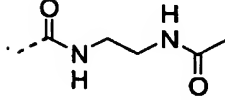
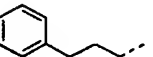
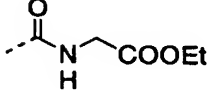
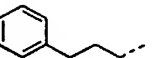
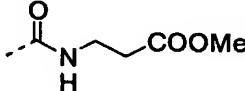
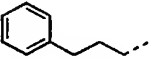
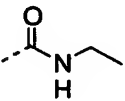
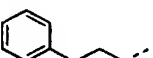
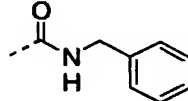
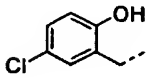
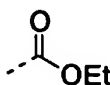
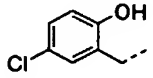
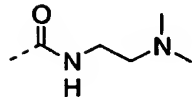
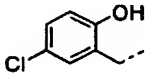
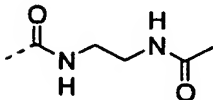
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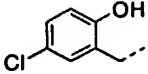
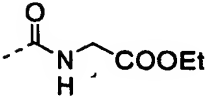
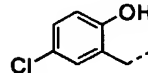
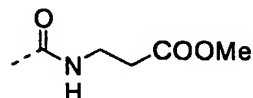
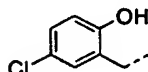
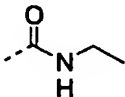
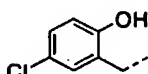
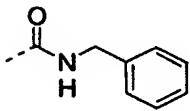
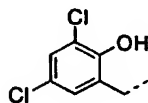
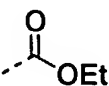
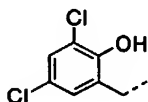
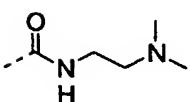
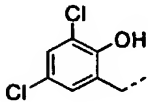
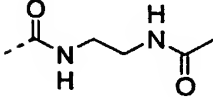
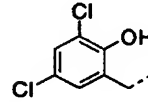
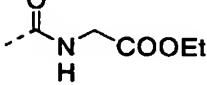
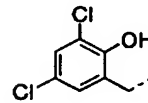
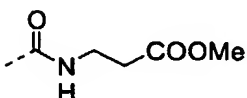
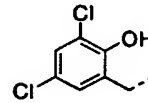
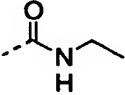
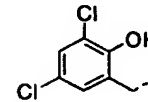
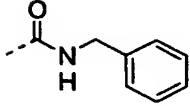
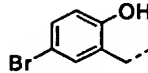
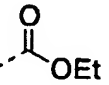
《表1-4》 X=単結合, q=0, r=0, Y=-(R4)C=C(R5)-

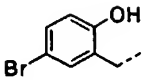
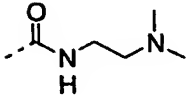
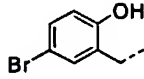
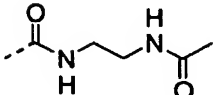
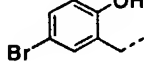
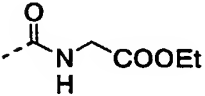
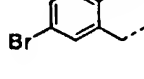
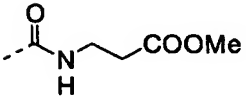
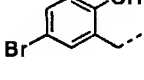
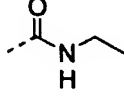
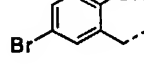
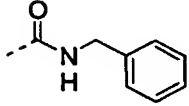
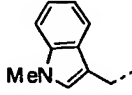
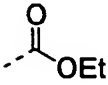
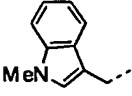
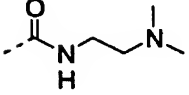
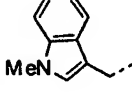
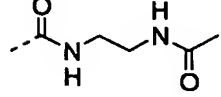
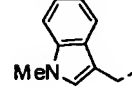
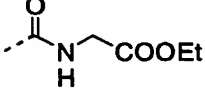
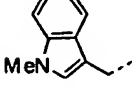
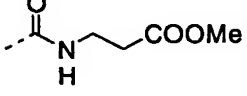
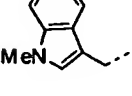
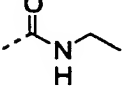
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1-4-2		H	H	H	H	H	
1-4-3		H	H	H	H	H	
1-4-4		H	H	H	H	H	
1-4-5		H	H	H	H	H	
1-4-6		H	H	H	H	H	
1-4-7		H	H	H	H	H	
1-4-8		H	H	H	H	H	
1-4-9		H	H	H	H	H	
1-4-10		H	H	H	H	H	
1-4-11		H	H	H	H	H	

1-4-12		H	H	H	H	H	
1-4-13		H	H	H	H	H	
1-4-14		H	H	H	H	H	
1-4-15		H	H	H	H	H	
1-4-16		H	H	H	H	H	
1-4-17		H	H	H	H	H	
1-4-18		H	H	H	H	H	
1-4-19		H	H	H	H	H	
1-4-20		H	H	H	H	H	
1-4-21		H	H	H	H	H	
1-4-22		H	H	H	H	H	
1-4-23		H	H	H	H	H	

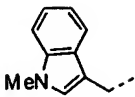
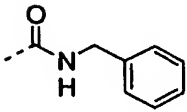
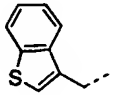
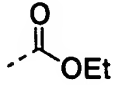
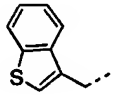
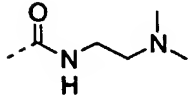
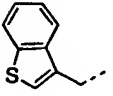
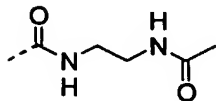
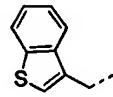
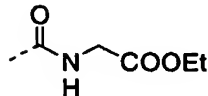
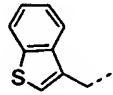
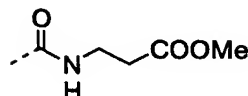
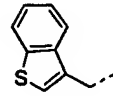
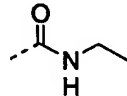
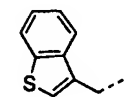
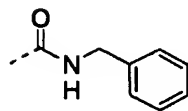
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1-4-26		H	H	H	H	H	
1-4-27		H	H	H	H	H	
1-4-28		H	H	H	H	H	
1-4-29		H	H	H	H	H	
1-4-30		H	H	H	H	H	
1-4-31		H	H	H	H	H	
1-4-32		H	H	H	H	H	
1-4-33		H	H	H	H	H	
1-4-34		H	H	H	H	H	
1-4-35		H	H	H	H	H	

1-4-36		H	H	H	H	H	
1-4-37		H	H	H	H	H	
1-4-38		H	H	H	H	H	
1-4-39		H	H	H	H	H	
1-4-40		H	H	H	H	H	
1-4-41		H	H	H	H	H	
1-4-42		H	H	H	H	H	
1-4-43		H	H	H	H	H	
1-4-44		H	H	H	H	H	
1-4-45		H	H	H	H	H	
1-4-46		H	H	H	H	H	
1-4-47		H	H	H	H	H	

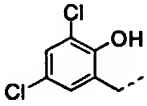
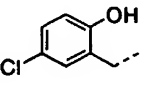
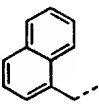
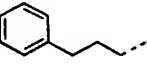
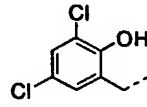
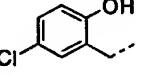
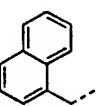
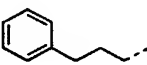
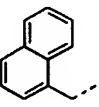
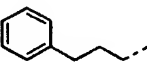
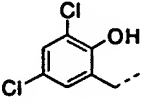
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1-4-49		H	H	H	H	H	
1-4-50		H	H	H	H	H	
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1-4-52		H	H	H	H	H	
1-4-53		H	H	H	H	H	
1-4-54		H	H	H	H	H	
1-4-55		H	H	H	H	H	
1-4-56		H	H	H	H	H	
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1-4-58		H	H	H	H	H	
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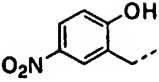
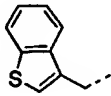
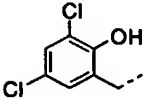
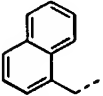
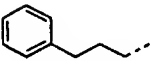
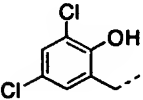
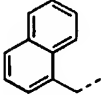
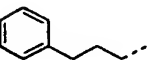
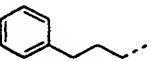
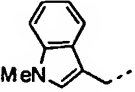
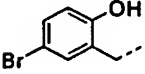
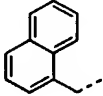
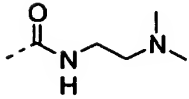
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1-4-64		H	H	H	H	H	
1-4-65		H	H	H	H	H	
1-4-66		H	H	H	H	H	
1-4-67		H	H	H	H	H	
1-4-68		H	H	H	H	H	
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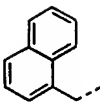
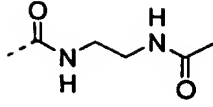
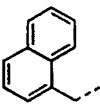
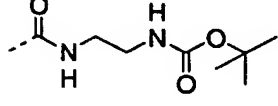
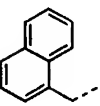
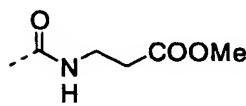
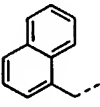
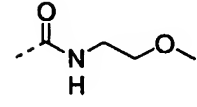
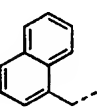
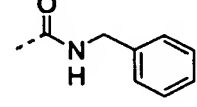
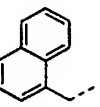
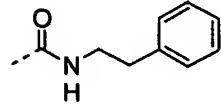
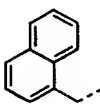
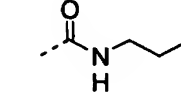
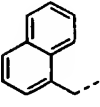
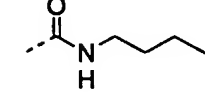
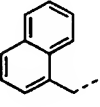
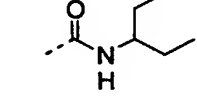
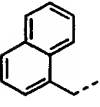
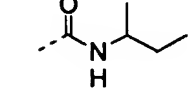
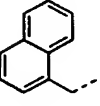
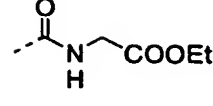
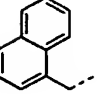
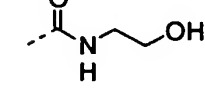


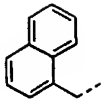
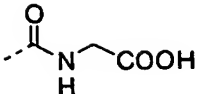
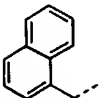
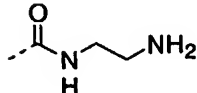
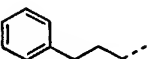
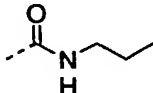
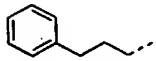
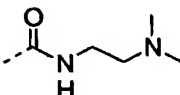
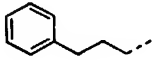
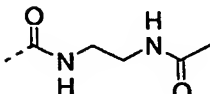
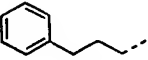
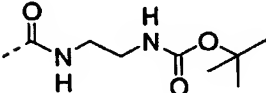
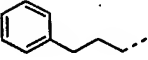
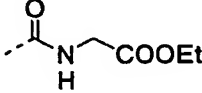
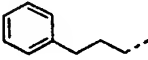
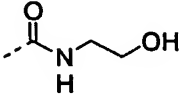
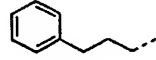
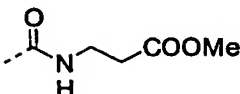
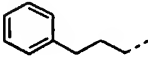
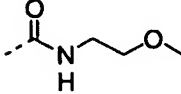
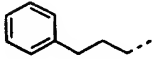
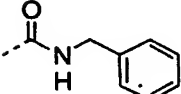
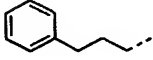
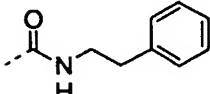
1-4-72		H	H	H	H	H	
1-4-73		H	H	H	H	H	
1-4-74		H	H	H	H	H	
1-4-75		H	H	H	H	H	
1-4-76		H	H	H	H	H	
1-4-77		H	H	H	H	H	
1-4-78		H	H	H	H	H	
1-4-79		H	H	H	H	H	

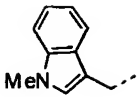
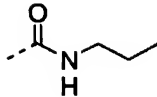
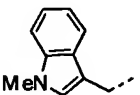
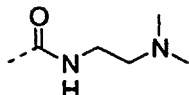
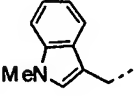
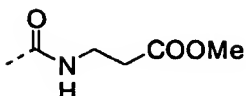
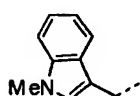
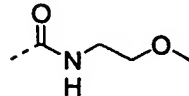
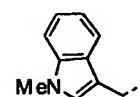
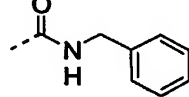
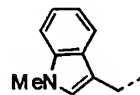
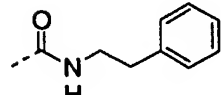
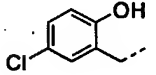
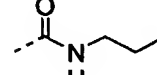
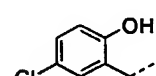
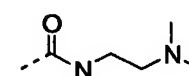
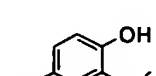
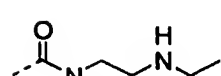
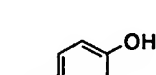
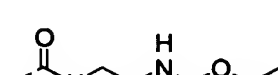
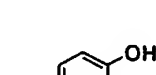

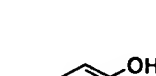

《表1-5》 X = 単結合, q = 0, r = 0, Y = -(R4)C=C(R5)-

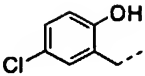
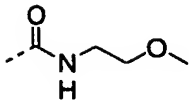
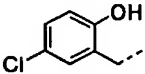
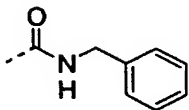
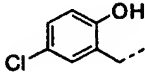
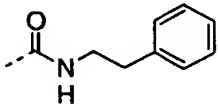
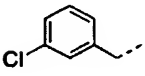
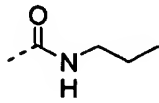
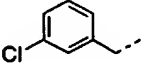
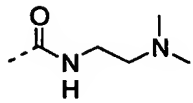
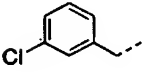
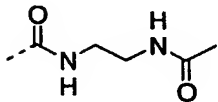
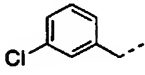
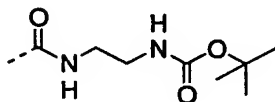
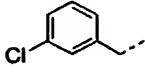
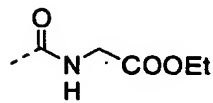
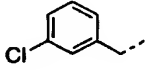
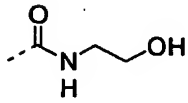
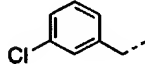
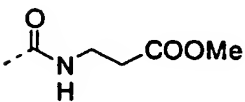
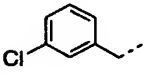
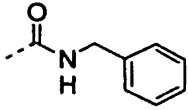
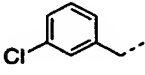
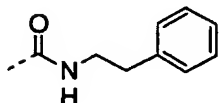
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1-5-2		H	H	H	H	COOEt	H
1-5-3		H	H	H	H	COOEt	H
1-5-4		H	H	H	H	COOEt	H
1-5-5		H	H	H	H	COOCH(Me)2	H
1-5-6		H	H	H	H	COOCH(Me)2	H
1-5-7		H	H	H	H	COOCH(Me)2	H
1-5-8		H	H	H	H	COOCH(Me)2	H
1-5-9		H	H	H	H	COOMe	H
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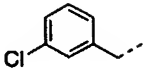
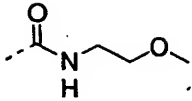

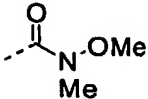
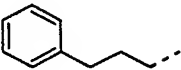
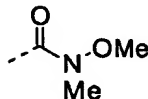
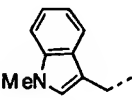
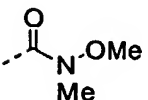
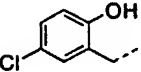
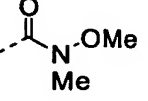
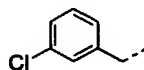
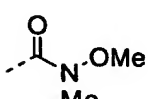
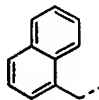
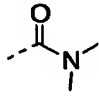
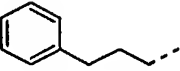
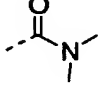
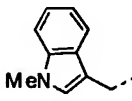
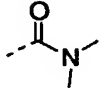
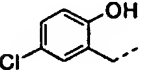
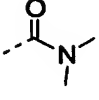
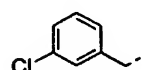
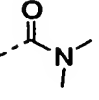
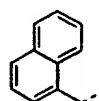
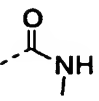
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1-5-14		H	Me	H	H	COOMe	H
1-5-15		H	Me	H	H	COOMe	H
1-5-16		H	Me	H	H	COOMe	H
1-5-17		H	Me	H	COOMe	H	H
1-5-18		H	Me	H	COOMe	H	H
1-5-19		H	Me	H	COOMe	H	H
1-5-20		H	H	H	H	COOH	H
1-5-21		H	H	H	H	COOH	H
1-5-22		H	H	H	H	COOH	H
1-5-23		H	H	H	H		H

1-5-24		H	H	H	H		H
1-5-25		H	H	H	H		H
1-5-26		H	H	H	H		H
1-5-27		H	H	H	H		H
1-5-28		H	H	H	H		H
1-5-29		H	H	H	H		H
1-5-30		H	H	H	H		H
1-5-31		H	H	H	H		H
1-5-32		H	H	H	H		H
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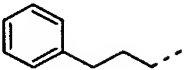

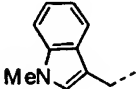

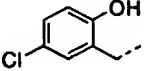

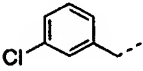

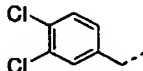
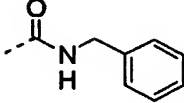
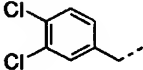
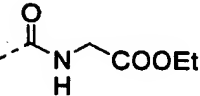
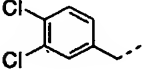
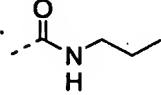
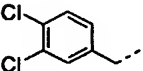
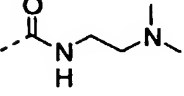
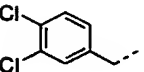
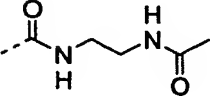
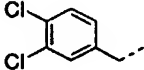
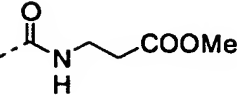
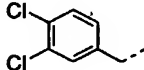
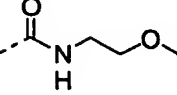
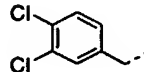
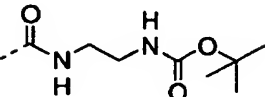
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1-5-37		H	H	H	H		H
1-5-38		H	H	H	H		H
1-5-39		H	H	H	H		H
1-5-40		H	H	H	H		H
1-5-41		H	H	H	H		H
1-5-42		H	H	H	H		H
1-5-43		H	H	H	H		H
1-5-44		H	H	H	H		H
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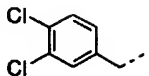
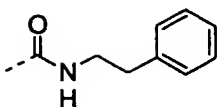
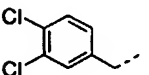
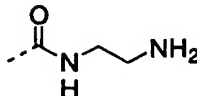
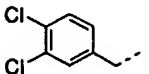
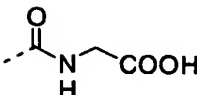
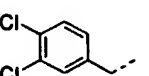
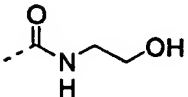
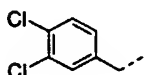
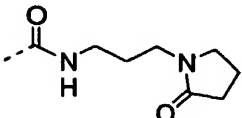
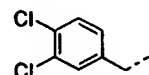
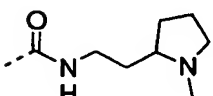
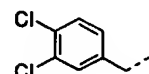
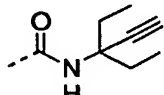
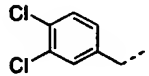
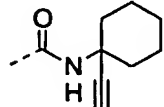
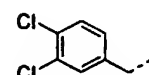
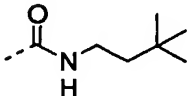
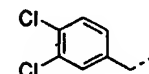
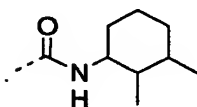
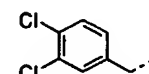
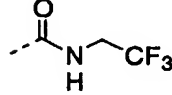
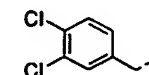
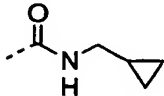
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1-5-50		H	H	H	H		H
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1-5-52		H	H	H	H		H
1-5-53		H	H	H	H		H
1-5-54		H	H	H	H		H
1-5-55		H	H	H	H		H
1-5-56		H	H	H	H		H
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1-5-59		H	H	H	H		H

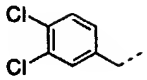
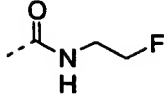
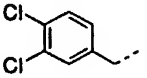
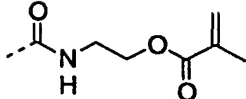
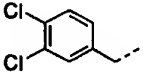
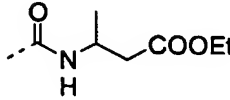
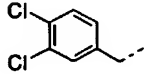
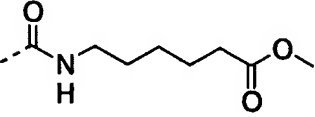
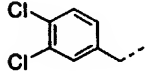
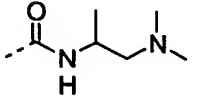
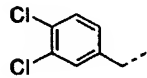
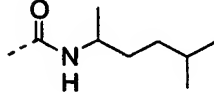
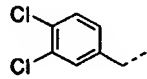
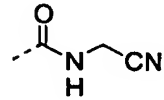
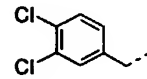
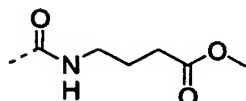
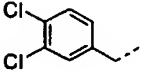
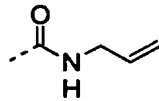
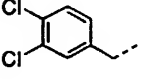
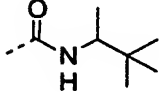
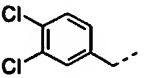
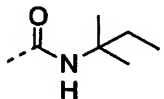
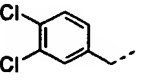
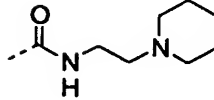
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1-5-67		H	H	H	H		H
1-5-68		H	H	H	H		H
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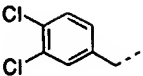
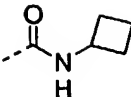
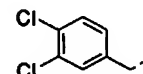
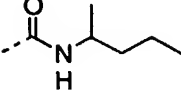
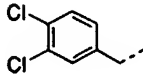
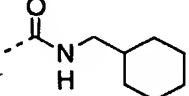
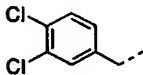
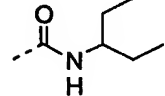
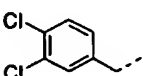
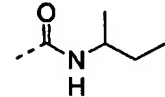
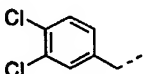
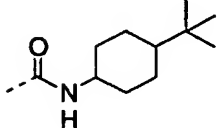
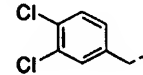
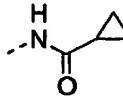
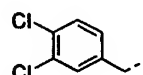
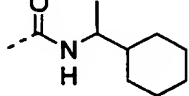
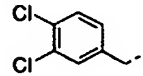
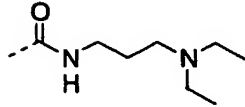
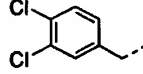
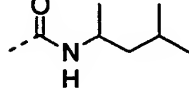
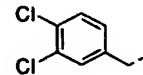
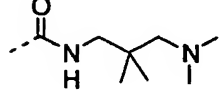
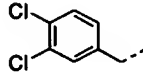
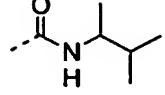
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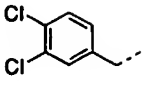
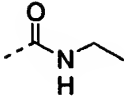
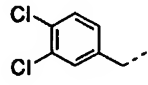
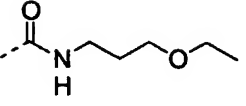
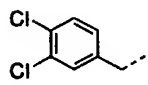
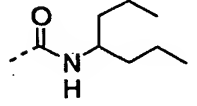
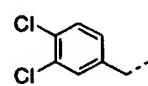
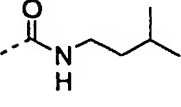
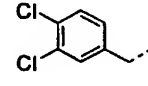
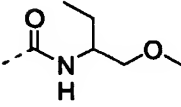
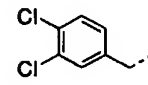
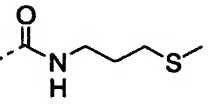
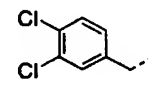
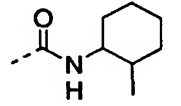
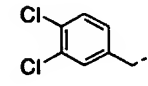
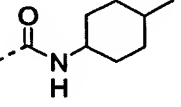
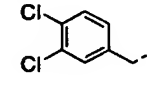
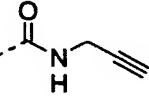
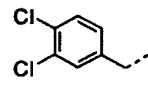
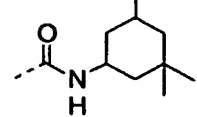
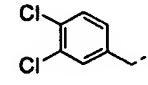
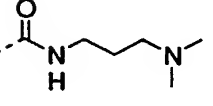
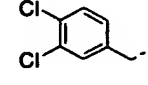
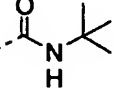


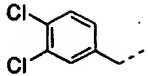
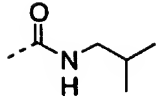
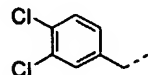
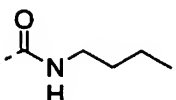
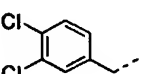
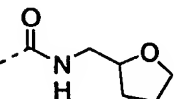
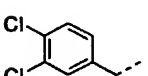
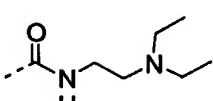
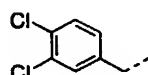
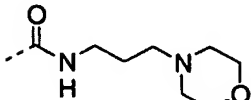
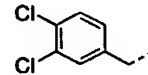
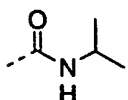
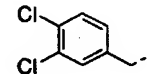
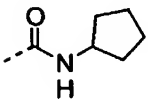
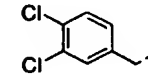
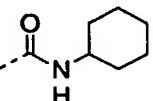
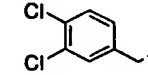
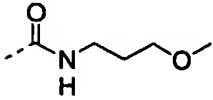
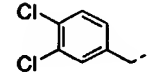
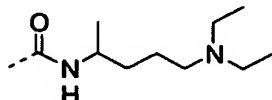
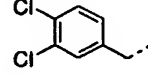
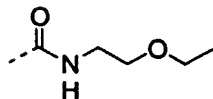
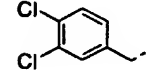
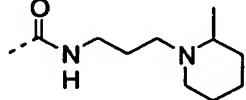
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1-5-89		H	H	H	H		H
1-5-90		H	H	H	H		H
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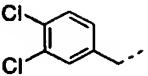
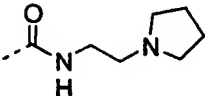
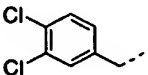
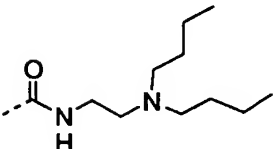
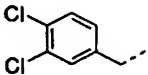
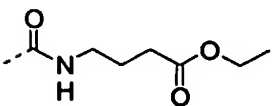
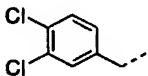
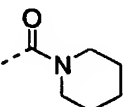
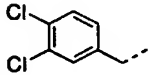
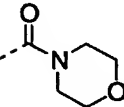
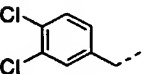
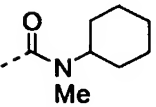
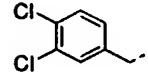
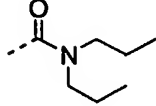
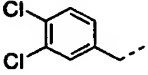
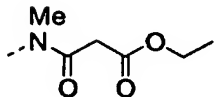
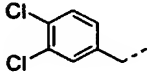
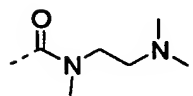
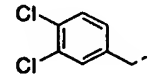
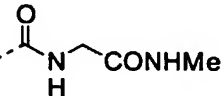
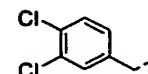
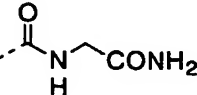
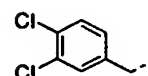
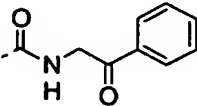
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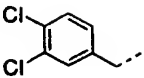
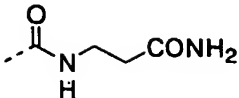
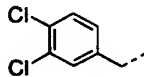
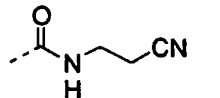
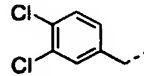
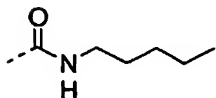
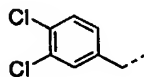
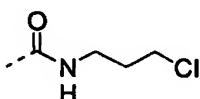
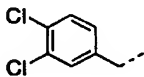
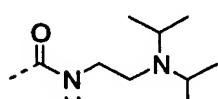
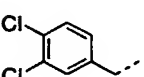
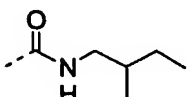
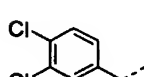
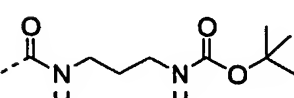
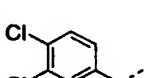
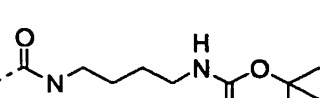
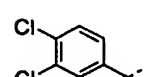
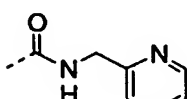
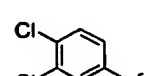
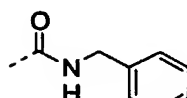
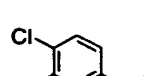
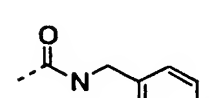
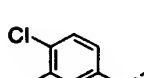
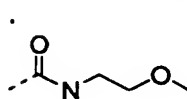
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1-5-113		H	H	H	H		H
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1-5-119		H	H	H	H		H

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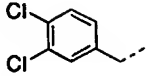
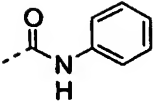
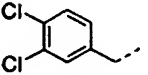
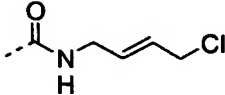
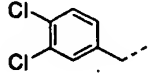
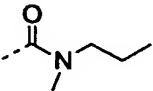
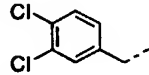
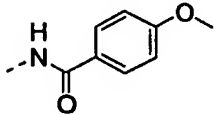












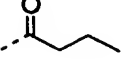
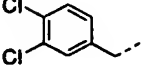
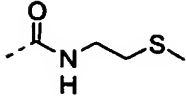
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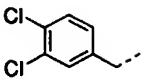
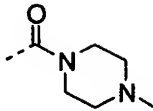
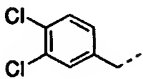
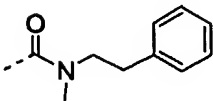
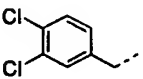
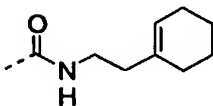
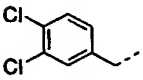
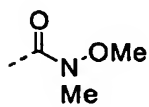
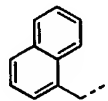
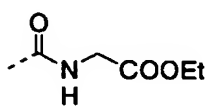
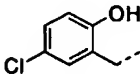
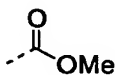
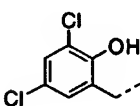
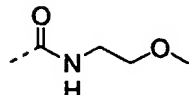
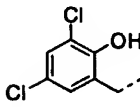
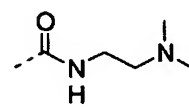
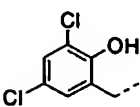
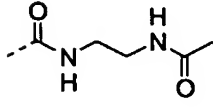
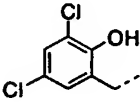
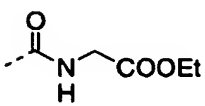
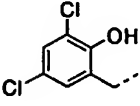
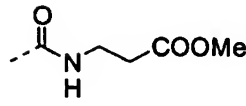
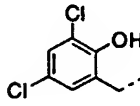
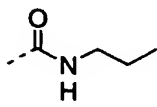
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1-5-148		H	H	H	H		H
1-5-149		H	H	H	H		H
1-5-150		H	H	H	H		H
1-5-151		H	H	H	H		H
1-5-152		H	H	H	H		H
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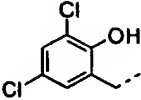
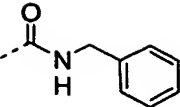
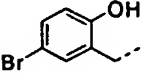
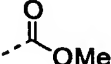
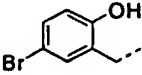
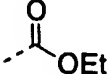
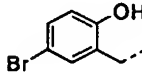
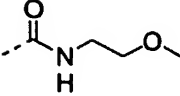
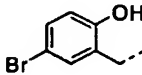
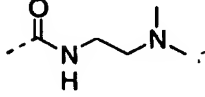
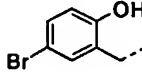
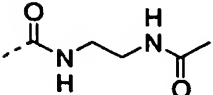
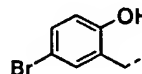
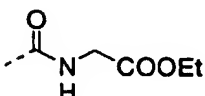
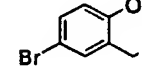
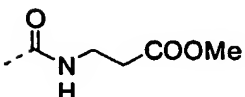
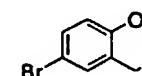
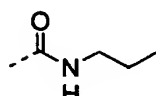
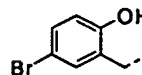
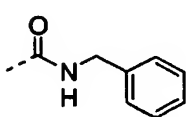
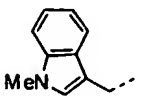
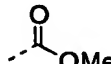
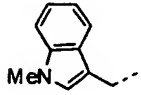
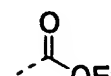
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1-5-160		H	H	H	H		H
1-5-161		H	H	H	H		H
1-5-162		H	H	H	H		H
1-5-163		H	H	H	H		H
1-5-164		H	H	H	H		H
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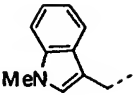
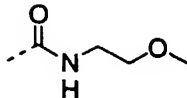
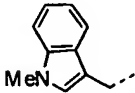
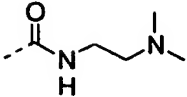
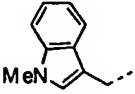
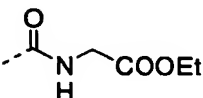
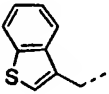
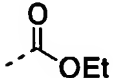
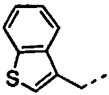
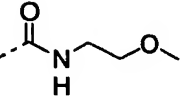
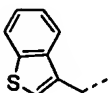
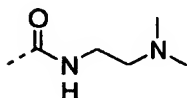
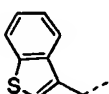
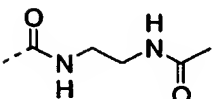
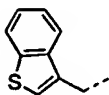
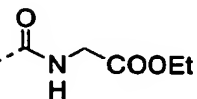
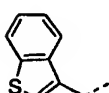
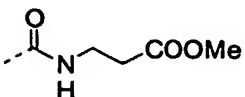
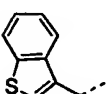
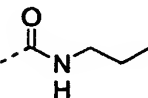
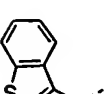
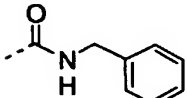
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1-5-172		H	H	H	H		H
1-5-173		H	H	H	H		H
1-5-174		H	H	H	H		H
1-5-175		H	H	H	H		H
1-5-176		H	H	H	H		H
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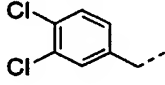
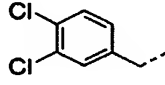
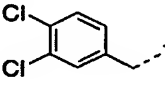
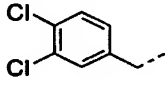
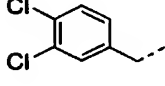
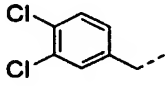
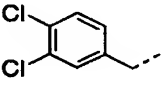
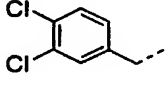
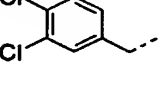
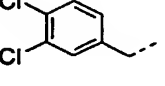
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1-5-183		H	H	H	H		H
1-5-184		H	H	H	H		H
1-5-185		H	H	H	H		H
1-5-186		H	H	H	H	CN	H
1-5-187		H	H	H	H		H
1-5-188		H	H	H	H		H
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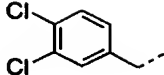
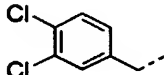
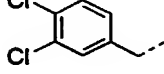
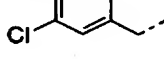
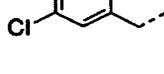
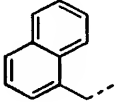
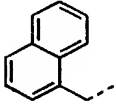
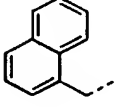
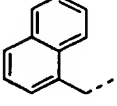
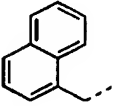
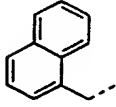
1-5-192		H	H	H	H		H
1-5-193		H	H	H	H		H
1-5-194		H	H	H	H		H
1-5-195		H	H	H	H		H
1-5-196		H	H	H	H		H
1-5-197		H	H	H	H		H
1-5-198		H	H	H	H		H
1-5-199		H	H	H	H		H
1-5-200		H	H	H	H		H
1-5-201		H	H	H	H		H
1-5-202		H	H	H	H		H
1-5-203		H	H	H	H		H

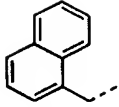
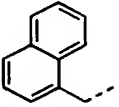
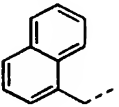
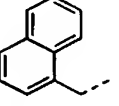
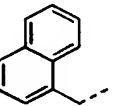
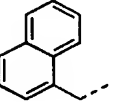
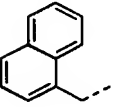
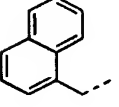
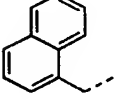
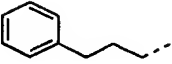
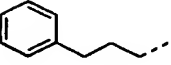
1-5-204		H	H	H	H		H
1-5-205		H	H	H	H		H
1-5-206		H	H	H	H		H
1-5-207		H	H	H	H		H
1-5-208		H	H	H	H		H
1-5-209		H	H	H	H		H
1-5-210		H	H	H	H		H
1-5-211		H	H	H	H		H
1-5-212		H	H	H	H		H
1-5-213		H	H	H	H		H
1-5-214		H	H	H	H		H
1-5-215		H	H	H	H		H

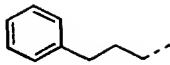
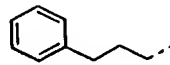
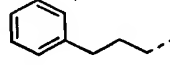
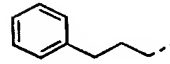
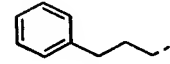
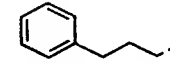
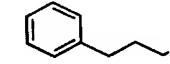
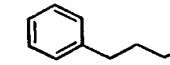
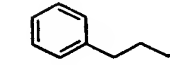
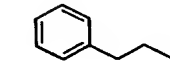
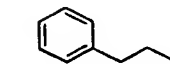
1-5-216		H	H	H	H		H
1-5-217		H	H	H	H		H
1-5-218		H	H	H	H		H
1-5-219		H	H	H	H		H
1-5-220		H	H	H	H		H
1-5-221		H	H	H	H		H
1-5-222		H	H	H	H		H
1-5-223		H	H	H	H		H
1-5-224		H	H	H	H		H
1-5-225		H	H	H	H		H
1-5-226		H	H	H	H		H

《表1-6》 X = 単結合, q = 0, r = 0, Y = -(R4)C=C(R5)-

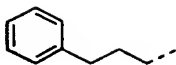
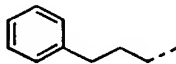
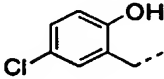
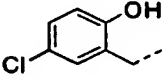
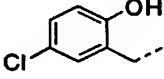
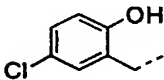
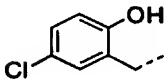
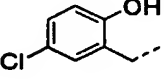
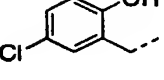
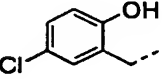
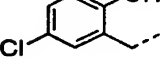
compnd NO.	R1	R2	R3	R4	R5	R6	R7
1-6-1		H	Et	H	H	H	H
1-6-2		Et	Et	H	H	H	H
1-6-3		CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H
1-6-4		H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H
1-6-5		(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	H	H	H	H
1-6-6		H	(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	H	H	H	H
1-6-7		(CH <sub>2</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	(CH <sub>2</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H
1-6-8		H	(CH <sub>2</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H
1-6-9		H	CH <sub>2</sub> COOMe	H	H	H	H
1-6-10		H	(CH <sub>2</sub> ) <sub>4</sub> COOEt	H	H	H	H

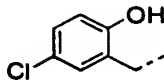
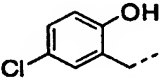
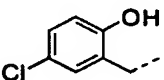
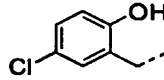
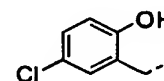
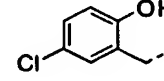
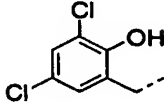
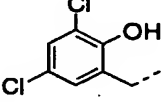
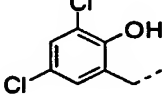
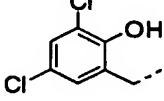
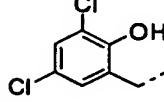
1-6-11		H	(CH <sub>2</sub> ) <sub>3</sub> NH <sub>2</sub>	H	H	H	H
1-6-12		H	(CH <sub>2</sub> ) <sub>2</sub> CONH <sub>2</sub>	H	H	H	H
1-6-13		H	(CH <sub>2</sub> ) <sub>2</sub> COOH	H	H	H	H
1-6-14		H	(CH <sub>2</sub> ) <sub>2</sub> CN	H	H	H	H
1-6-15		H	(CH <sub>2</sub> ) <sub>2</sub> COOEt	H	H	H	H
1-6-16		H	Et	H	H	H	H
1-6-17		Et	Et	H	H	H	H
1-6-18		CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H
1-6-19		H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H
1-6-20		(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	H	H	H	H
1-6-21		H	(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	H	H	H	H

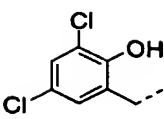
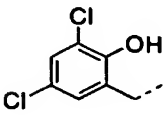
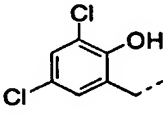
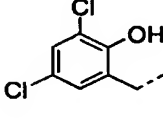
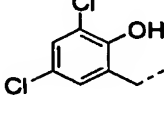
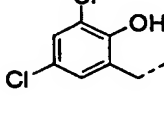
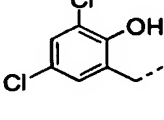
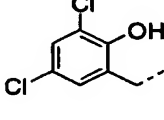
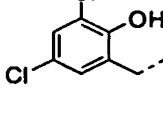
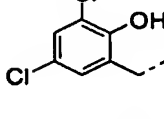
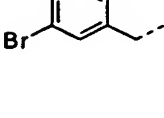
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1-6-23		H	(CH <sub>2</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H
1-6-24		H	CH <sub>2</sub> COOMe	H	H	H	H
1-6-25		H	(CH <sub>2</sub> ) <sub>4</sub> COOEt	H	H	H	H
1-6-26		H	(CH <sub>2</sub> ) <sub>3</sub> NH <sub>2</sub>	H	H	H	H
1-6-27		H	(CH <sub>2</sub> ) <sub>2</sub> CONH <sub>2</sub>	H	H	H	H
1-6-28		H	(CH <sub>2</sub> ) <sub>2</sub> COOH	H	H	H	H
1-6-29		H	(CH <sub>2</sub> ) <sub>2</sub> CN	H	H	H	H
1-6-30		H	(CH <sub>2</sub> ) <sub>2</sub> COOEt	H	H	H	H
1-6-31		H	Et	H	H	H	H
1-6-32		Et	Et	H	H	H	H

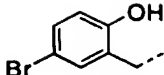
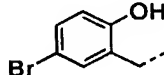
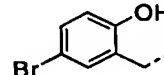
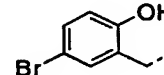
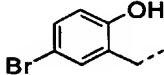
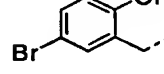
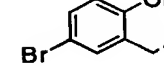
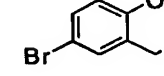
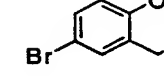
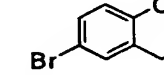
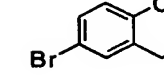
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1-6-40		H	(CH <sub>2</sub> ) <sub>4</sub> COOEt	H	H	H	H
1-6-41		H	(CH <sub>2</sub> ) <sub>3</sub> NH <sub>2</sub>	H	H	H	H
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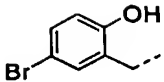
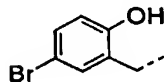
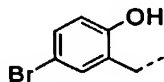
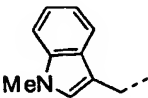
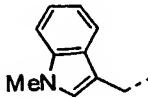
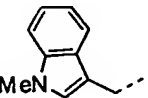
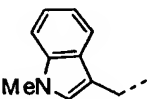
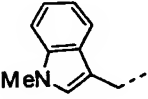
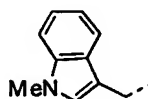
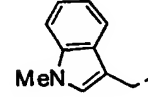
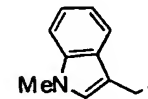


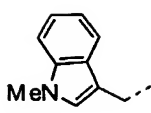
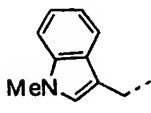
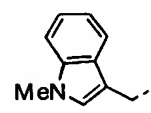
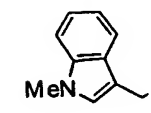
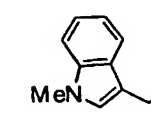
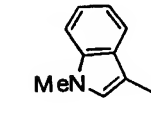
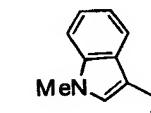
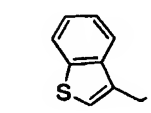
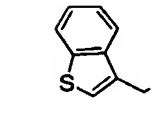
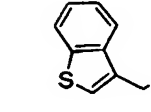
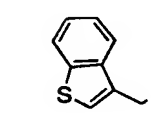
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1-6-46		H	Et	H	H	H	H
1-6-47		Et	Et	H	H	H	H
1-6-48		CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H
1-6-49		H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H
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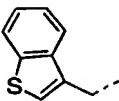
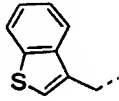
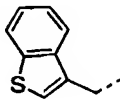
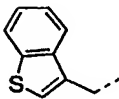
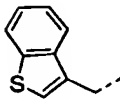
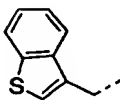
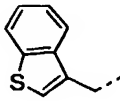
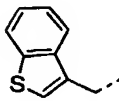
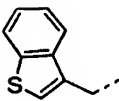
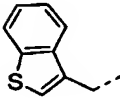
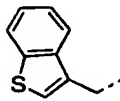
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1-6-59		H	(CH <sub>2</sub> ) <sub>2</sub> CN	H	H	H	H
1-6-60		H	(CH <sub>2</sub> ) <sub>2</sub> COOEt	H	H	H	H
1-6-61		H	Et	H	H	H	H
1-6-62		Et	Et	H	H	H	H
1-6-63		CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H
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1-6-76		H	Et	H	H	H	H

1-6-77		Et	Et	H	H	H	H
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1-6-86		H	(CH <sub>2</sub> ) <sub>3</sub> NH <sub>2</sub>	H	H	H	H
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1-6-91		H	Et	H	H	H	H
1-6-92		Et	Et	H	H	H	H
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1-6-106		H	Et	H	H	H	H
1-6-107		Et	Et	H	H	H	H
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1-6-109		H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H

1-6-110		(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	H	H	H	H
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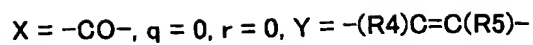
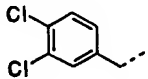
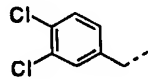
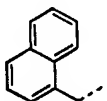
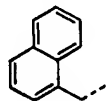
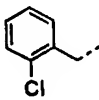
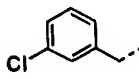
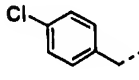
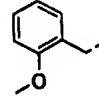
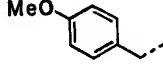
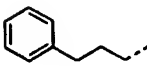
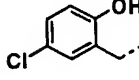
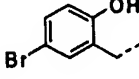
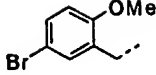
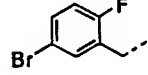
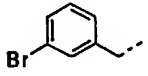
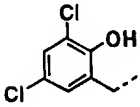
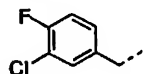
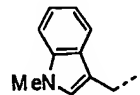
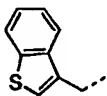
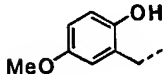
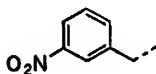
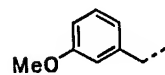
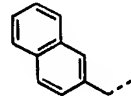
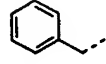
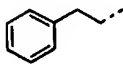


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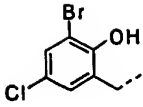
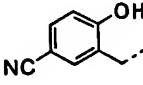
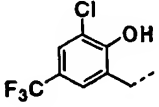
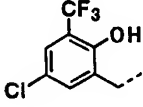
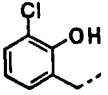
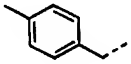
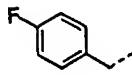
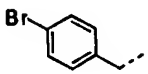
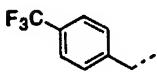
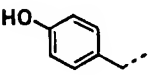
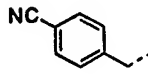
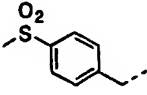
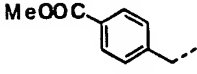
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1		H	H	H	H	H	H
2		H	H	H	Cl	H	H
3		H	H	H	H	H	H
4		H	H	H	Cl	H	H
5		H	H	H	H	H	H
6		H	H	H	H	H	H
7		H	H	H	H	H	H
8		H	H	H	H	H	H
9		H	H	H	H	H	H
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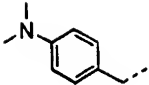
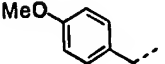
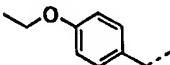
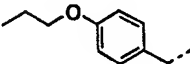
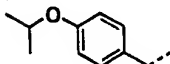
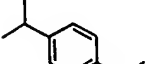
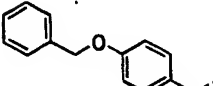
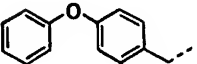
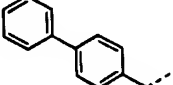
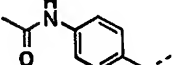
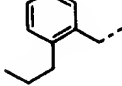
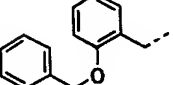

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


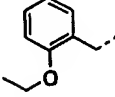
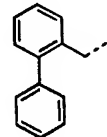
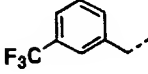
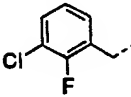
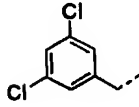
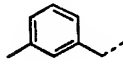
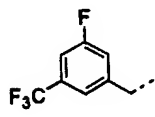
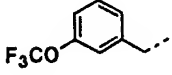
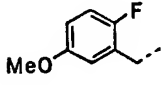
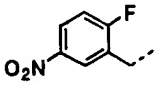
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17		H	H	H	H	H	H
18		H	H	H	H	H	H
19		H	H	H	H	H	H
20		H	H	H	H	H	H
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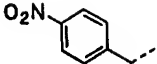
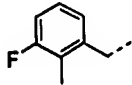
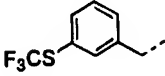
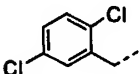
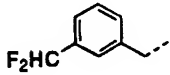

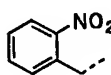
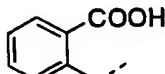
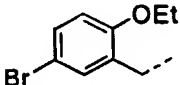
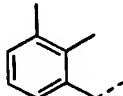
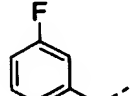
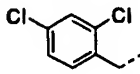
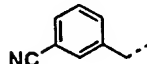
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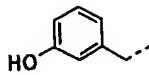
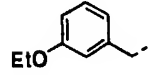
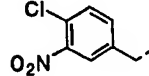
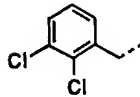
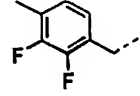
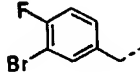
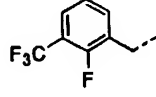
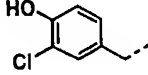
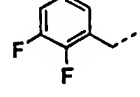
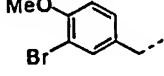
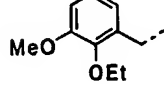
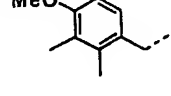
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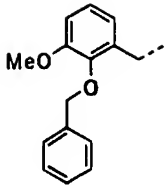
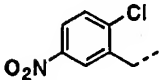
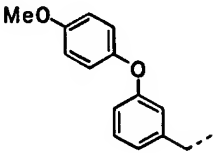
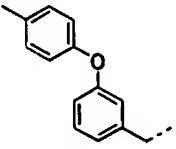
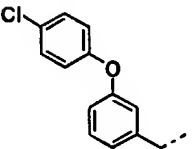
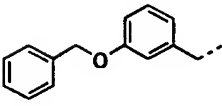
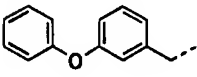
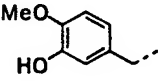
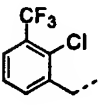
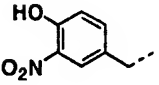
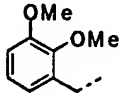
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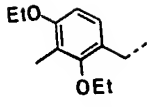
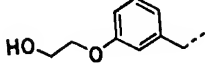
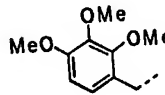
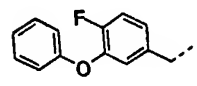
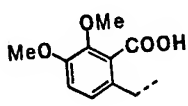
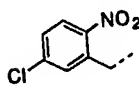
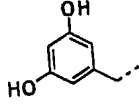
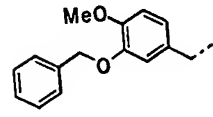
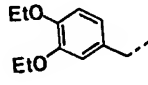
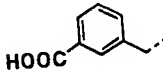
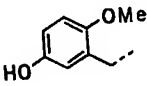
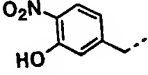
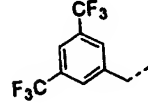
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129

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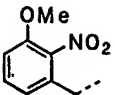
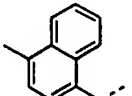
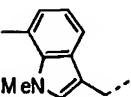
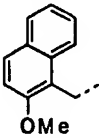
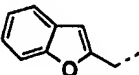
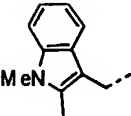

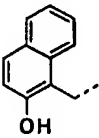
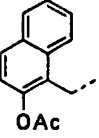
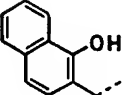

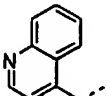
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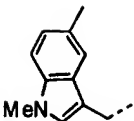
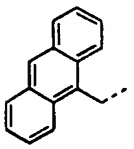
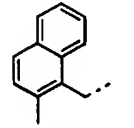
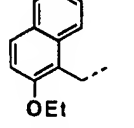
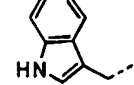
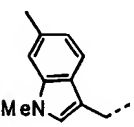
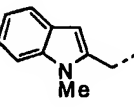
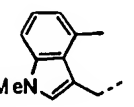
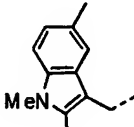
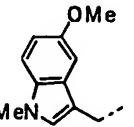
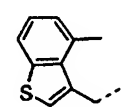
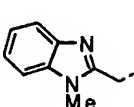
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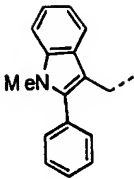
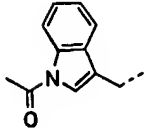
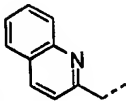
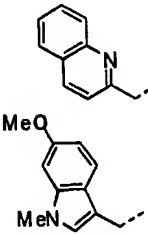
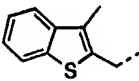
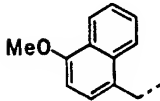
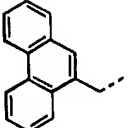
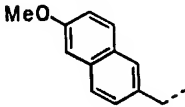
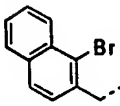
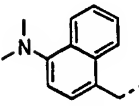
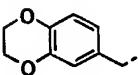
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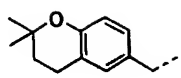
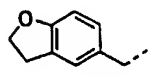
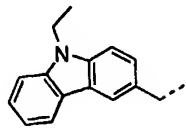
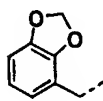
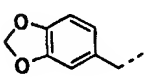
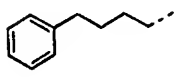
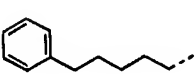
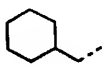
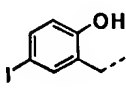
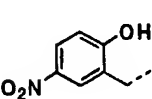
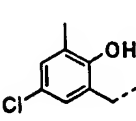
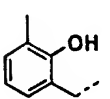
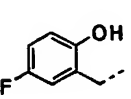
132

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130		H	H	H	H	H	H
131		H	H	H	H	H	H
132		H	H	H	H	H	H
133		H	H	H	H	H	H
134		H	H	H	H	H	H
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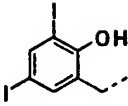
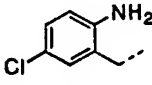

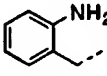
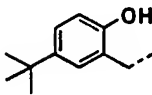
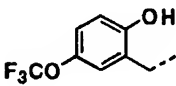
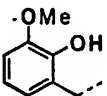
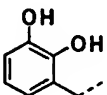
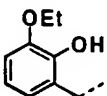
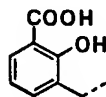
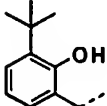


133

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142		H	H	H	H	H	H
143		H	H	H	H	H	H
144		H	H	H	H	H	H
145		H	H	H	H	H	H
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

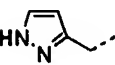
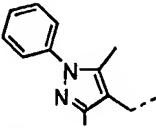
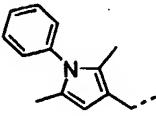
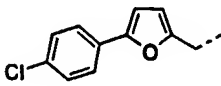





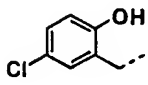
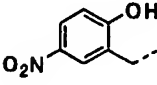
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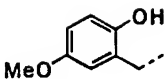
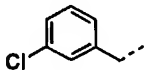
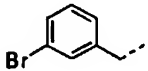
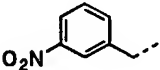
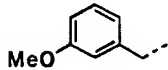
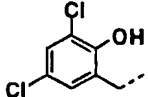
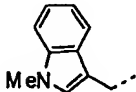
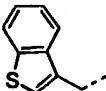
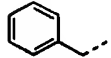
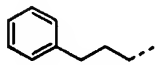
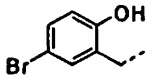
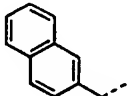
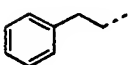
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155		H	H	H	H	H	H
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157		H	H	H	H	H	H
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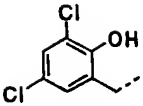
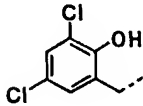
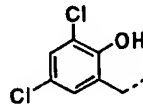
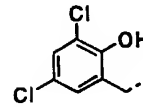
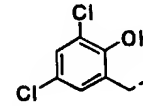
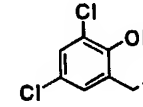
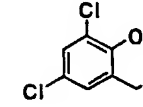
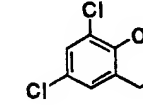
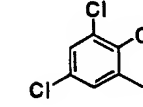
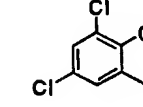
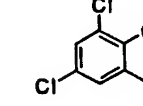
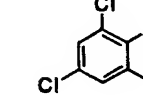
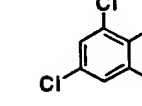
135

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136

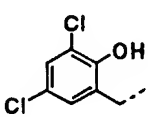
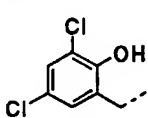
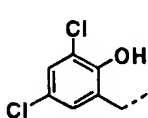
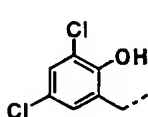
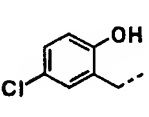
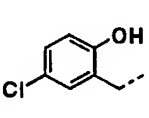
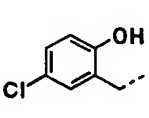
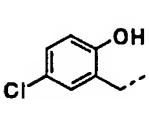
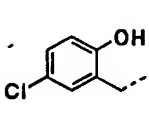
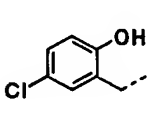
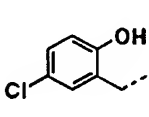
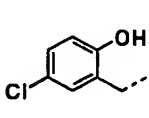
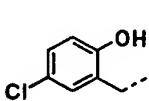
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187		H	H	H	Cl	H	H

188		H	H	H	Cl	H	H
189		H	H	H	Cl	H	H
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192		H	H	H	Cl	H	H
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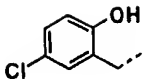
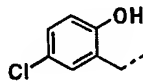
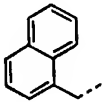
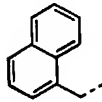
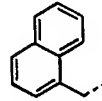
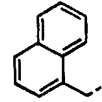
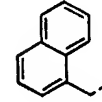
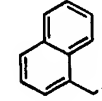
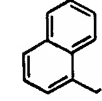
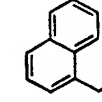
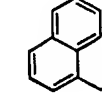
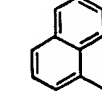
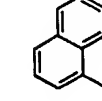
201		H	H	Cl	H	H	H
202		H	H	H	OMe	H	H
203		H	H	H	COOMe	H	H
204		H	H	H	H	Cl	H
205		H	H	H	H	COOMe	H
206		H	H	H	H	H	Cl
207		H	H	H	OCF3	H	H
208		H	H	COOMe	H	H	H
209		H	H	H	CF3	H	H
210		H	H	H	Me	H	H
211		H	H	H	F	H	H
212		H	H	H	OH	H	H
213		H	H	H	NO2	H	H



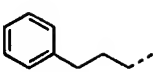
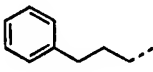
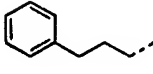
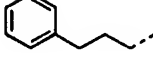
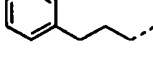
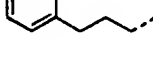
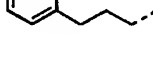
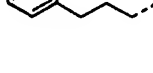
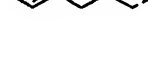

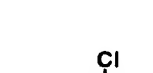
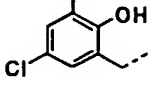
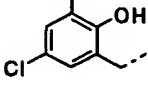
139

214		H	H	H	F	F	H
215		H	H	F	H	H	H
216		H	H	Me	H	H	H
217		H	H	H	CN	H	H
218		H	H	Cl	H	H	H
219		H	H	H	OMe	H	H
220		H	H	H	COOMe	H	H
221		H	H	H	H	Cl	H
222		H	H	H	H	COOMe	H
223		H	H	H	H	H	Cl
224		H	H	H	OCF3	H	H
225		H	H	COOMe	H	H	H
226		H	H	H	CF3	H	H

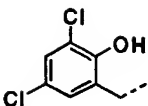
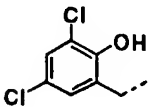
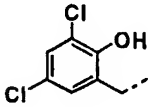
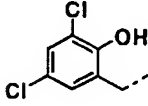
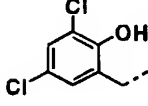
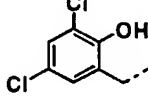
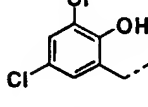
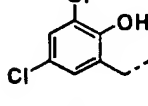
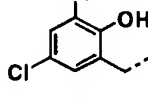
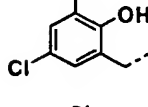
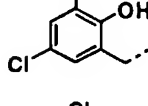
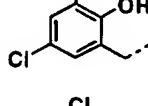
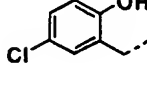
140

227		H	H	H	Me	H	H
228		H	H	H	F	H	H
229		H	H	Cl	H	H	H
230		H	H	H	OMe	H	H
231		H	H	H	COOMe	H	H
232		H	H	H	H	Cl	H
233		H	H	H	H	COOMe	H
234		H	H	H	H	H	Cl
235		H	H	H	OCF3	H	H
236		H	H	COOMe	H	H	H
237		H	H	H	CF3	H	H
238		H	H	H	Me	H	H
239		H	H	H	F	H	H

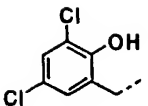
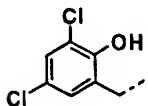
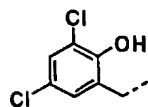
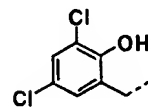
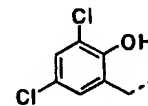
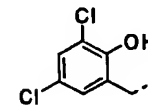
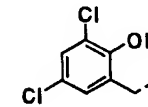
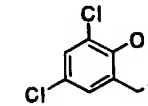
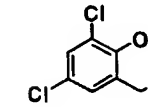
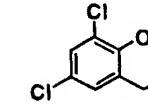
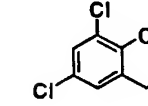
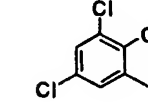
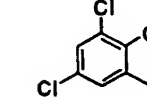
141

240		H	H	Cl	H	H	H
241		H	H	H	OMe	H	H
242		H	H	H	COOMe	H	H
243		H	H	H	H	Cl	H
244		H	H	H	H	COOMe	H
245		H	H	H	H	H	Cl
246		H	H	H	OCF3	H	H
247		H	H	COOMe	H	H	H
248		H	H	H	CF3	H	H
249		H	H	H	Me	H	H
250		H	H	H	F	H	H
251		H	H	H	H	H	COOMe
252		H	H	H	H	F	H

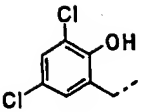
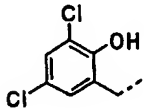
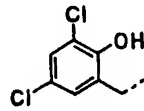
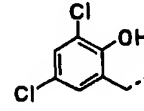
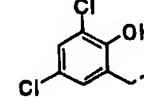
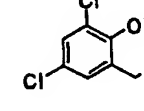
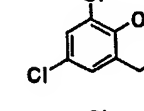
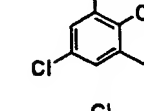
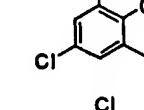
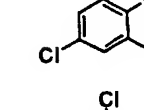
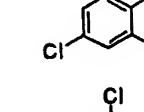
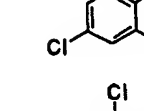
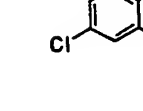
142

253		H	H	H	H	H	F
254		H	H	H	H	Me	H
255		H	H	H	H	H	Me
256		H	H	OMe	H	H	H
257		H	H	H	H	OMe	H
258		H	H	H	H	H	OMe
259		H	H	CF3	H	H	H
260		H	H	H	H	CF3	H
261		H	H	H	H	H	CF3
262		H	H	OH	H	H	H
263		H	H	H	H	OH	H
264		H	H	H	H	H	OH
265		H	H	OCF3	H	H	H

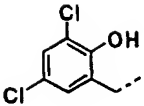
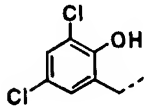
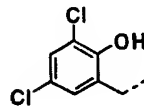
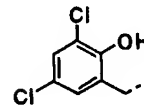
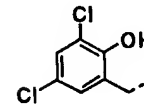
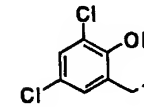
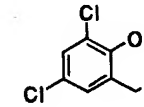
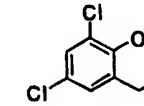
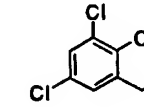
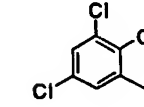
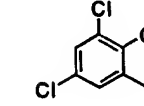
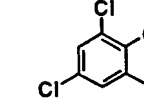
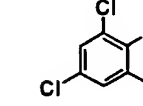
143

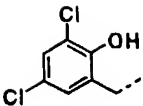
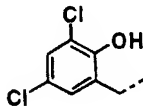
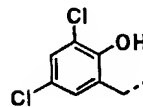
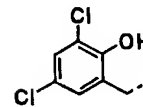
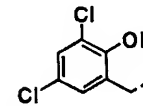
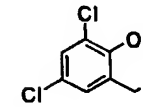
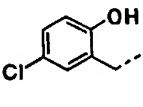
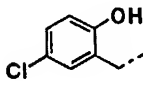
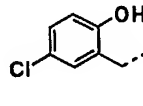
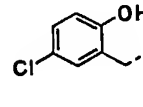
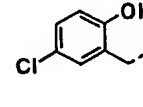
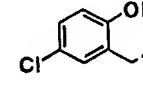
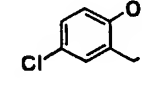
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268		H	H	NO2	H	H	H
269		H	H	H	H	NO2	H
270		H	H	H	H	H	NO2
271		H	H	CN	H	H	H
272		H	H	H	H	CN	H
273		H	H	H	H	H	CN
274		H	H	Br	H	H	H
275		H	H	H	Br	H	H
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278		H	H	COOH	H	H	H

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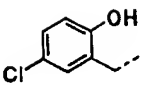
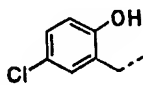
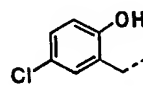
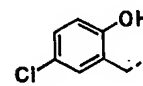
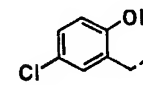
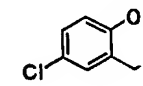
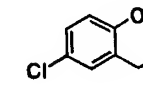
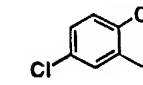
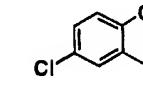
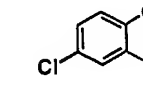
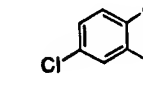
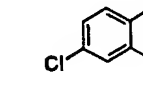
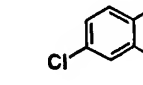
279		H	H	H	COOH	H	H
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281		H	H	H	H	H	COOH
282		H	H	NHCOMe	H	H	H
283		H	H	H	NHCOMe	H	H
284		H	H	H	H	NHCOMe	H
285		H	H	H	H	H	NHCOMe
286		H	H	SO2NH2	H	H	H
287		H	H	H	SO2NH2	H	H
288		H	H	H	H	SO2NH2	H
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290		H	H	Me	Me	H	H
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145

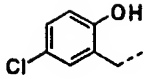
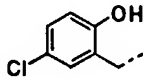
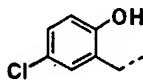
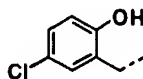
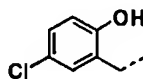
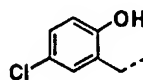
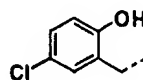
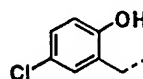
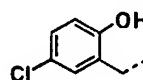
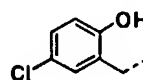
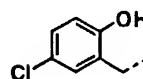
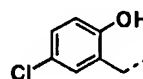
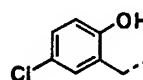
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294		H	H	F	H	F	H
295		H	H	H	F	F	H
296		H	H	Cl	Cl	H	H
297		H	H	Cl	H	Cl	H
298		H	H	H	Cl	Cl	H
299		H	H	Me	F	H	H
300		H	H	Me	Cl	H	H
301		H	H	Me	OH	H	H
302		H	H	Me	OMe	H	H
303		H	H	F	Me	H	H
304		H	H	F	Cl	H	H

305		H	H	F	OH	H	H
306		H	H	F	OMe	H	H
307		H	H	Cl	Me	H	H
308		H	H	Cl	F	H	H
309		H	H	Cl	OH	H	H
310		H	H	Cl	OMe	H	H
311		H	H	H	H	H	COOMe
312		H	H	F	H	H	H
313		H	H	H	H	F	H
314		H	H	H	H	H	F
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317		H	H	H	H	H	Me

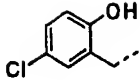
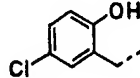
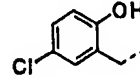
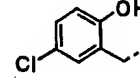
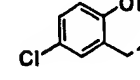
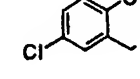
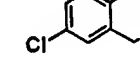
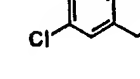
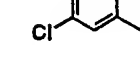
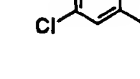
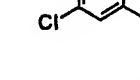
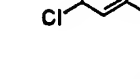
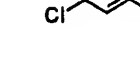


318		H	H	OMe	H	H	H
319		H	H	H	H	OMe	H
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321		H	H	CF3	H	H	H
322		H	H	H	H	CF3	H
323		H	H	H	H	H	CF3
324		H	H	OH	H	H	H
325		H	H	H	OH	H	H
326		H	H	H	H	OH	H
327		H	H	H	H	H	OH
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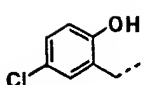
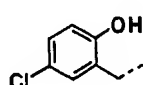
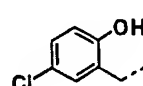
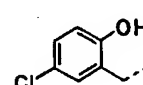
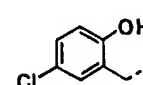
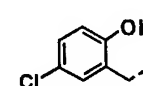
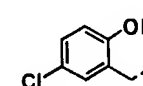
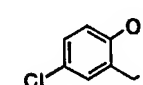
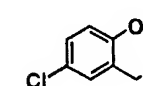
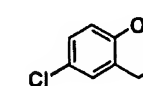
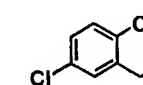
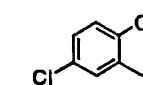
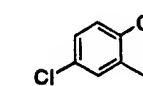
148

331		H	H	NO2	H	H	H
332		H	H	H	NO2	H	H
333		H	H	H	H	NO2	H
334		H	H	H	H	H	NO2
335		H	H	CN	H	H	H
336		H	H	H	CN	H	H
337		H	H	H	H	CN	H
338		H	H	H	H	H	CN
339		H	H	Br	H	H	H
340		H	H	H	Br	H	H
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343		H	H	COOH	H	H	H

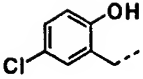
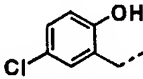
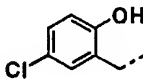
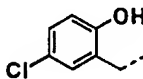
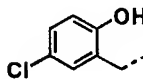
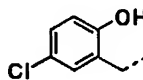
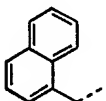
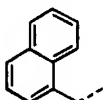
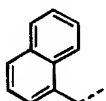
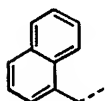
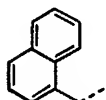
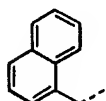
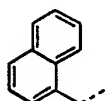
149



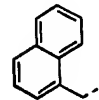
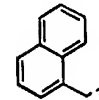

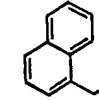
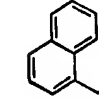


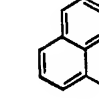
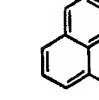


344		H	H	H	COOH	H	H
345		H	H	H	H	COOH	H
346		H	H	H	H	H	COOH
347		H	H	NHCOMe	H	H	H
348		H	H	H	NHCOMe	H	H
349		H	H	H	H	NHCOMe	H
350		H	H	H	H	H	NHCOMe
351		H	H	SO2NH2	H	H	H
352		H	H	H	SO2NH2	H	H
353		H	H	H	H	SO2NH2	H
354		H	H	H	H	H	SO2NH2
355		H	H	Me	Me	H	H
356		H	H	Me	H	Me	H

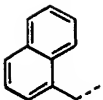
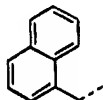
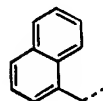
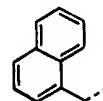
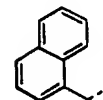
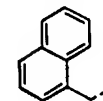
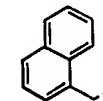
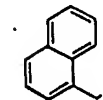
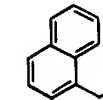
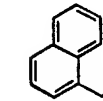
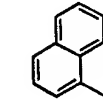
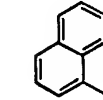
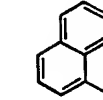
150

357		H	H	H	Me	Me	H
358		H	H	F	F	H	H
359		H	H	F	H	F	H
360		H	H	H	F	F	H
361		H	H	Cl	Cl	H	H
362		H	H	Cl	H	Cl	H
363		H	H	H	Cl	Cl	H
364		H	H	Me	F	H	H
365		H	H	Me	Cl	H	H
366		H	H	Me	OH	H	H
367		H	H	Me	OMe	H	H
368		H	H	F	Me	H	H
369		H	H	F	Cl	H	H

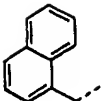
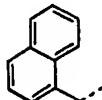
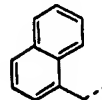
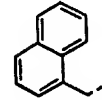
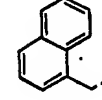
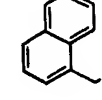
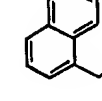
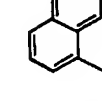
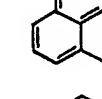
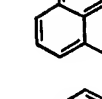
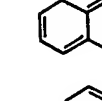
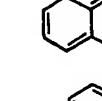
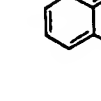
151

370		H	H	F	OH	H	H
371		H	H	F	OMe	H	H
372		H	H	Cl	Me	H	H
373		H	H	Cl	F	H	H
374		H	H	Cl	OH	H	H
375		H	H	Cl	OMe	H	H
376		H	H	H	H	H	COOMe
377		H	H	F	H	H	H
378		H	H	H	H	F	H
379		H	H	H	H	H	F
380		H	H	Me	H	H	H
381		H	H	H	H	Me	H
382		H	H	H	H	H	Me

383		H	H	OMe	H	H	H
384		H	H	H	H	OMe	H
385		H	H	H	H	H	OMe
386		H	H	CF3	H	H	H
387		H	H	H	H	CF3	H
388		H	H	H	H	H	CF3
389		H	H	OH	H	H	H
390		H	H	H	OH	H	H
391		H	H	H	H	OH	H
392		H	H	H	H	H	OH
393		H	H	OCF3	H	H	H
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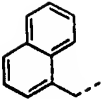
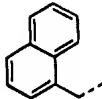
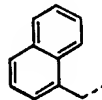
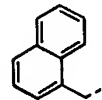
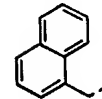
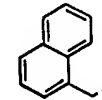
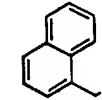
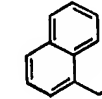
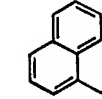
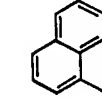
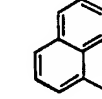
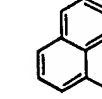
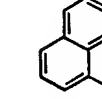
396		H	H	NO2	H	H	H
397		H	H	H	NO2	H	H
398		H	H	H	H	NO2	H
399		H	H	H	H	H	NO2
400		H	H	CN	H	H	H
401		H	H	H	CN	H	H
402		H	H	H	H	CN	H
403		H	H	H	H	H	CN
404		H	H	Br	H	H	H
405		H	H	H	Br	H	H
406		H	H	H	H	Br	H
407		H	H	H	H	H	Br
408		H	H	COOH	H	H	H

154







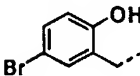
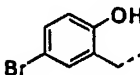
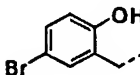
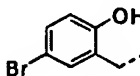
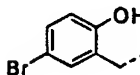
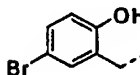
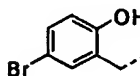
409		H	H	H	COOH	H	H
410		H	H	H	H	COOH	H
411		H	H	H	H	H	COOH
412		H	H	NHCOMe	H	H	H
413		H	H	H	NHCOMe	H	H
414		H	H	H	H	NHCOMe	H
415		H	H	H	H	H	NHCOMe
416		H	H	SO <sub>2</sub> NH <sub>2</sub>	H	H	H
417		H	H	H	SO <sub>2</sub> NH <sub>2</sub>	H	H
418		H	H	H	H	SO <sub>2</sub> NH <sub>2</sub>	H
419		H	H	H	H	H	SO <sub>2</sub> NH <sub>2</sub>
420		H	H	Me	Me	H	H
421		H	H	Me	H	Me	H



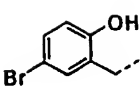
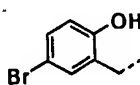
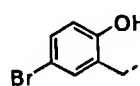
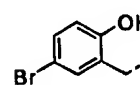
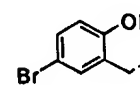
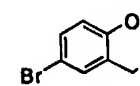
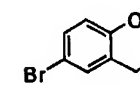
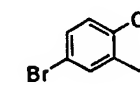
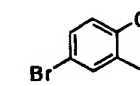
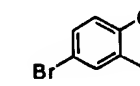
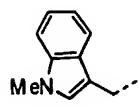
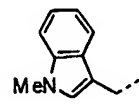
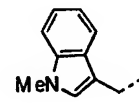
155

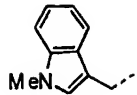
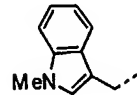
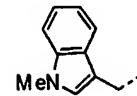
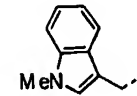
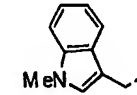
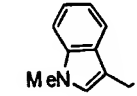
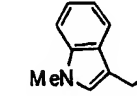
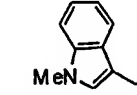
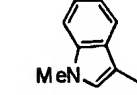
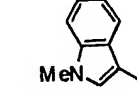
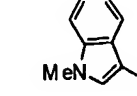
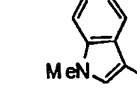
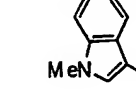
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423		H	H	F	F	H	H
424		H	H	F	H	F	H
425		H	H	H	F	F	H
426		H	H	Cl	Cl	H	H
427		H	H	Cl	H	Cl	H
428		H	H	H	Cl	Cl	H
429		H	H	Me	F	H	H
430		H	H	Me	Cl	H	H
431		H	H	Me	OH	H	H
432		H	H	Me	OMe	H	H
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434		H	H	F	Cl	H	H

156

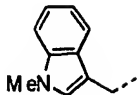
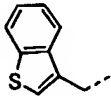
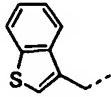
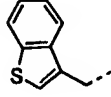
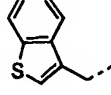
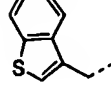
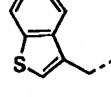
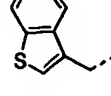
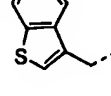
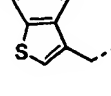
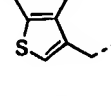
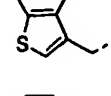
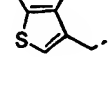
435		H	H	F	OH	H	H
436		H	H	F	OMe	H	H
437		H	H	Cl	Me	H	H
438		H	H	Cl	F	H	H
439		H	H	Cl	OH	H	H
440		H	H	Cl	OMe	H	H
441		H	H	Cl	H	H	H
442		H	H	H	OMe	H	H
443		H	H	H	COOMe	H	H
444		H	H	H	H	Cl	H
445		H	H	H	H	COOMe	H
446		H	H	H	H	H	Cl
447		H	H	H	OCF3	H	H

157

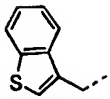
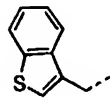
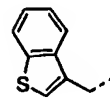
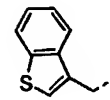
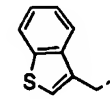
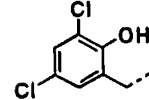
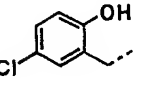
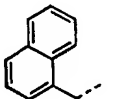
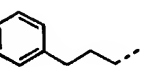
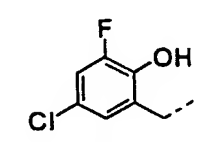
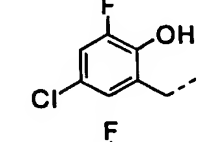
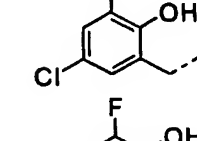
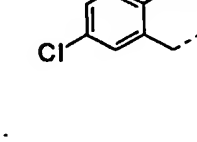
448		H	H	COOMe	H	H	H
449		H	H	H	CF3	H	H
450		H	H	H	Me	H	H
451		H	H	H	F	H	H
452		H	H	H	OH	H	H
453		H	H	H	NO2	H	H
454		H	H	H	F	F	H
455		H	H	F	H	H	H
456		H	H	Me	H	H	H
457		H	H	H	CN	H	H
458		H	H	Cl	H	H	H
459		H	H	H	OMe	H	H
460		H	H	H	COOMe	H	H

461		H	H	H	H	Cl	H
462		H	H	H	H	COOMe	H
463		H	H	H	H	H	Cl
464		H	H	H	OCF3	H	H
465		H	H	COOMe	H	H	H
466		H	H	H	CF3	H	H
467		H	H	H	Me	H	H
468		H	H	H	F	H	H
469		H	H	H	OH	H	H
470		H	H	H	NO2	H	H
471		H	H	H	F	F	H
472		H	H	F	H	H	H
473		H	H	Me	H	H	H

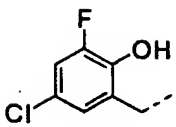
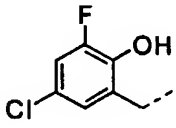
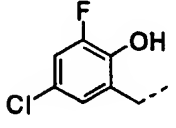
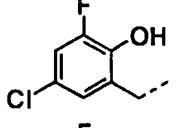
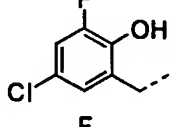
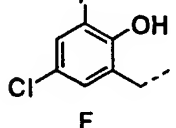
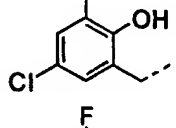
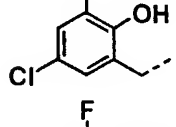
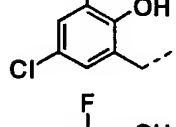
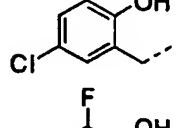
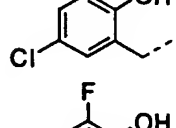
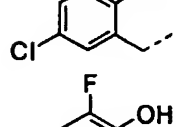
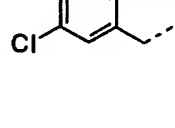
159

474		H	H	H	CN	H	H
475		H	H	Cl	H	H	H
476		H	H	H	OMe	H	H
477		H	H	H	COOMe	H	H
478		H	H	H	H	Cl	H
479		H	H	H	H	COOMe	H
480		H	H	H	H	H	Cl
481		H	H	H	OCF3	H	H
482		H	H	COOMe	H	H	H
483		H	H	H	CF3	H	H
484		H	H	H	Me	H	H
485		H	H	H	F	H	H
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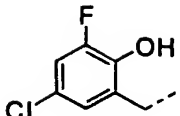
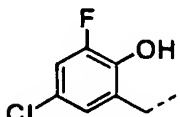
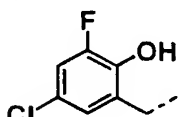
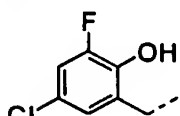
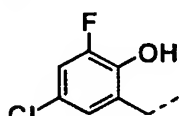
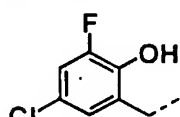
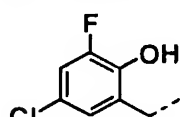
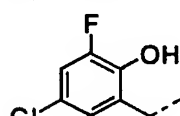
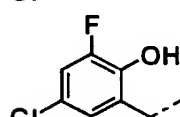
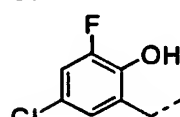
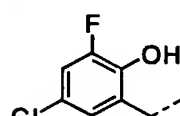
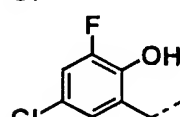
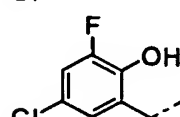
160

487		H	H	H	NO2	H	H
488		H	H	H	F	F	H
489		H	H	F	H	H	H
490		H	H	Me	H	H	H
491		H	H	H	CN	H	H
492		H	Me	H	H	H	H
493		H	Me	H	H	H	H
494		H	Me	H	H	H	H
495		H	Me	H	H	H	H
496		H	H	H	H	H	H
497		H	H	F	H	H	H
498		H	H	Cl	H	H	H
499		H	H	Me	H	H	H

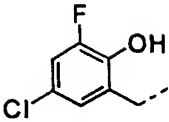
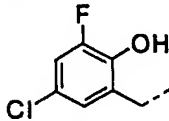
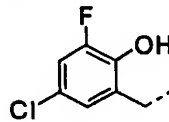
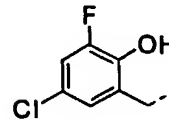
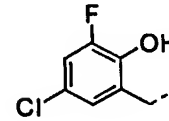
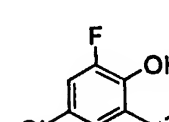
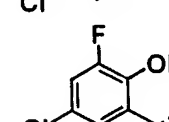
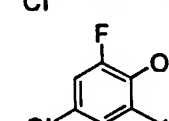
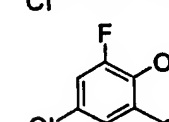
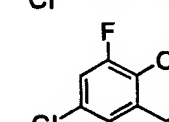
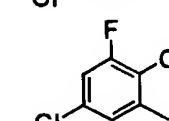
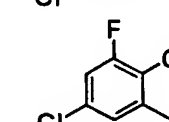
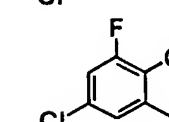
161

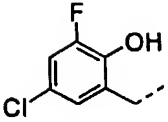
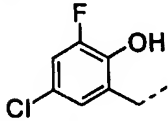
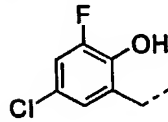
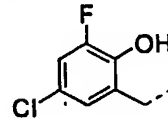
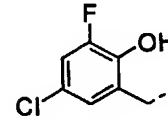
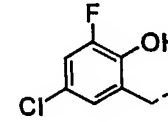
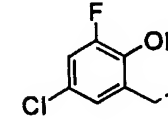
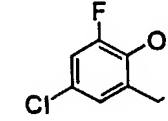
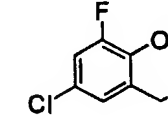
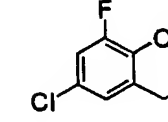
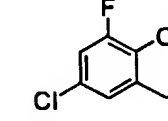
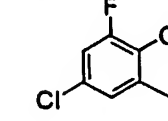
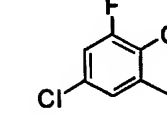
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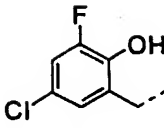
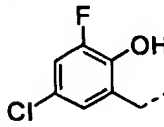
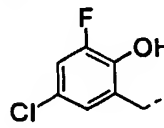
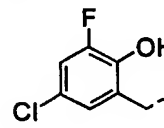
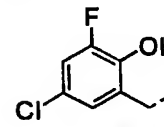
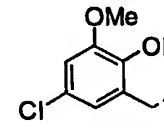
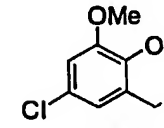
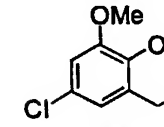
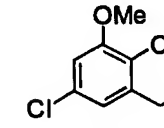
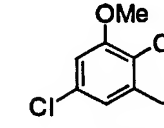
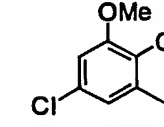
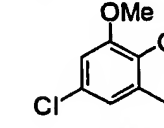
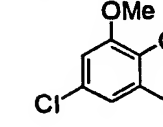
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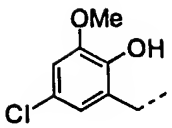
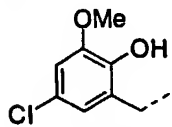
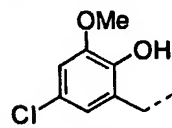
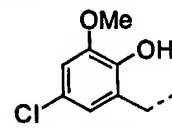
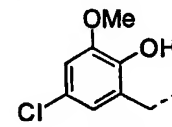
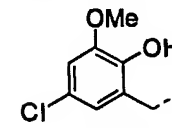
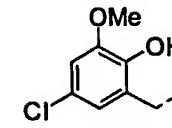
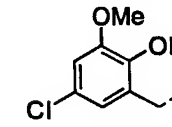
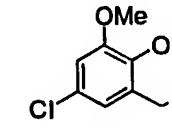
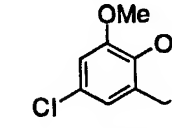
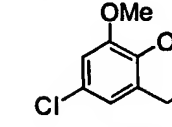
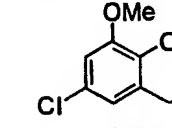
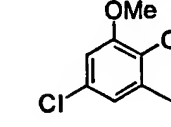
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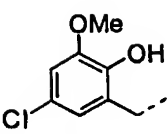
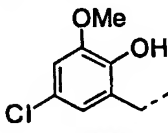
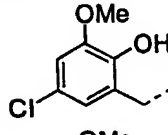
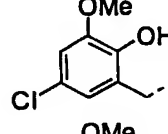
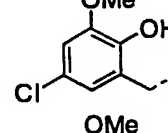
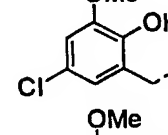
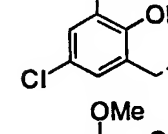
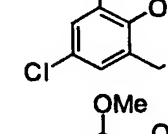
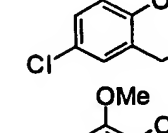
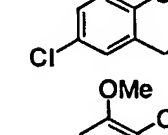
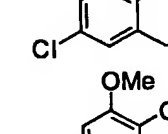
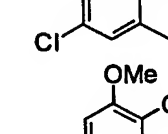
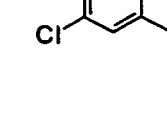
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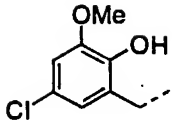
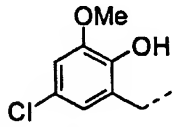
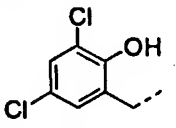
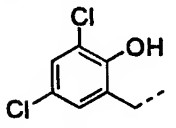
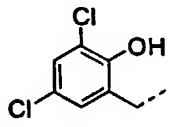
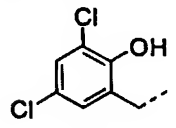
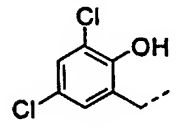
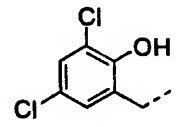
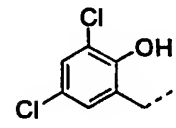
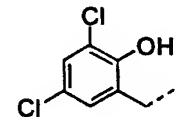
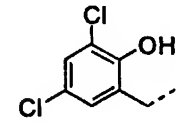
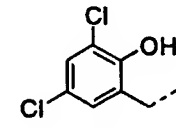
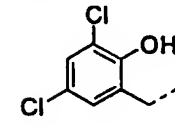
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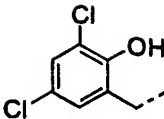
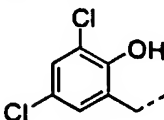
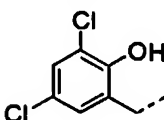
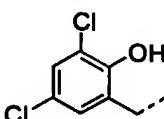
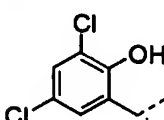
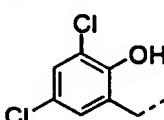
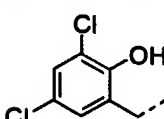
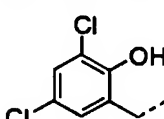
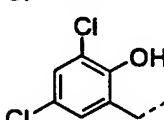
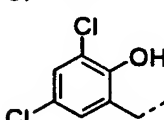
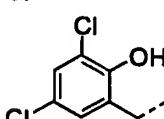
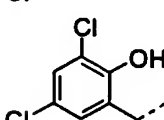
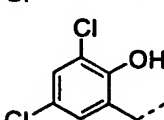
166

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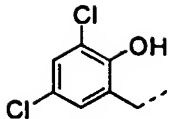
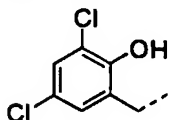
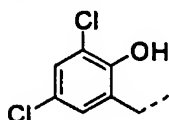
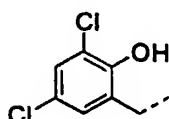
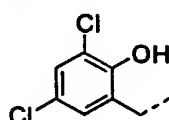
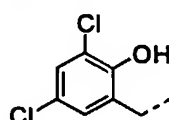
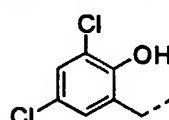
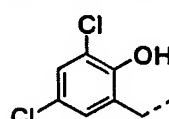
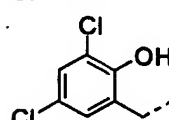
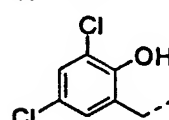
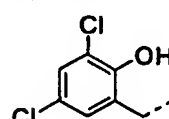
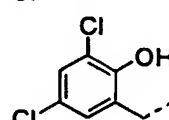
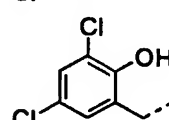
167

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582		H	H	Me	OMe	H	H
583		H	H	Et	F	H	H
584		H	H	Et	Cl	H	H
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586		H	H	Et	Et	H	H
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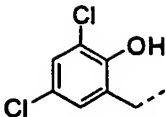
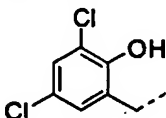
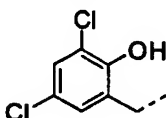
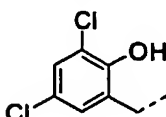
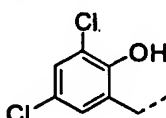
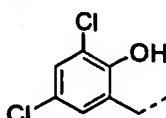
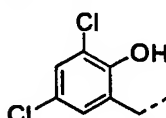
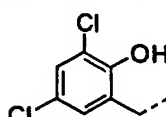
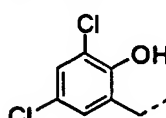
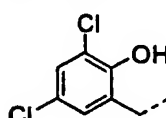
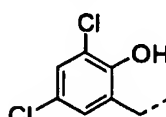
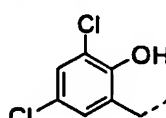
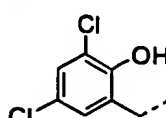
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595		H	H	H	CN	H	Me
596		H	H	Me	Br	H	H
597		H	H	H	Br	Me	H
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599		H	H	Me	H	F	H
600		H	H	Me	H	H	F
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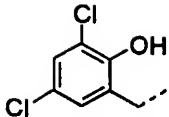
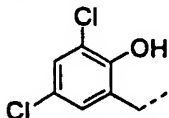
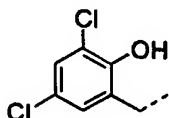
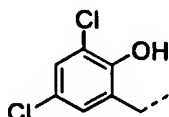
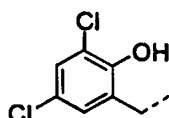
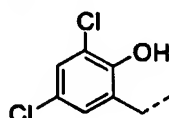
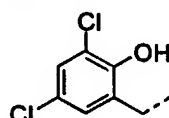
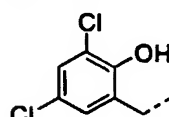
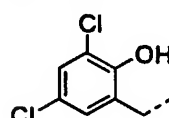
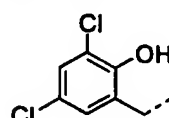
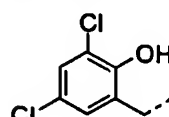
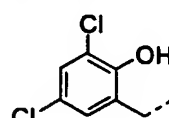
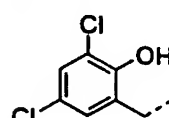
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608		H	H	H	H	NH2	H
609		H	H	Et	H	H	H
610		H	H	H	Et	H	H
611		H	H	H	H	Et	H
612		H	H	iPr	H	H	H
613		H	H	H	iPr	H	H
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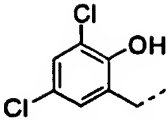
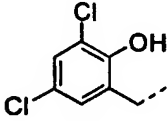
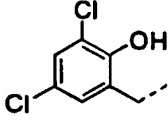
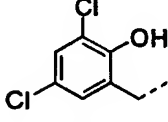
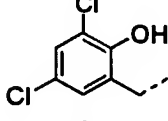
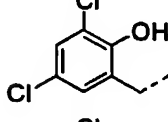
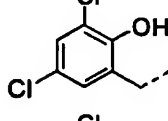
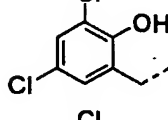
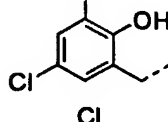
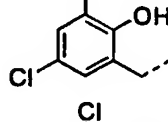
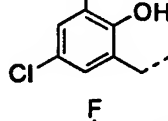
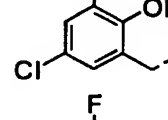
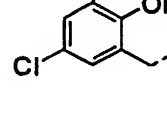
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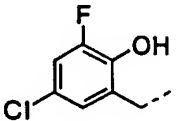
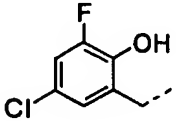
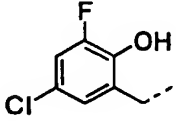
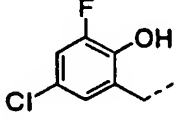
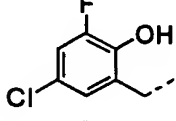
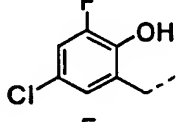
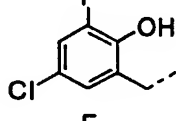
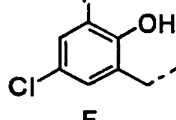
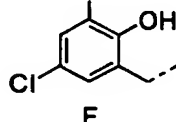
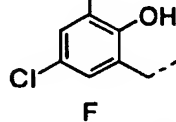
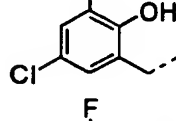
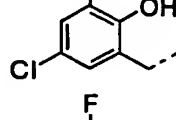
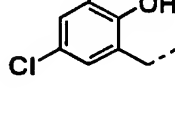
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623		H	H	H	H	OiPr	H
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625		H	H	H	OPh	H	H
626		H	H	H	H	OPh	H
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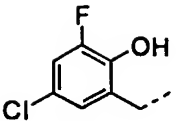
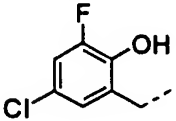
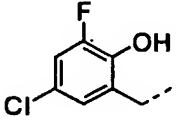
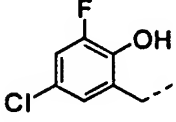
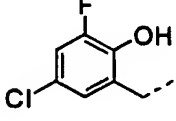
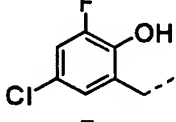
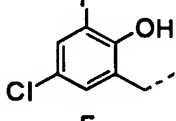
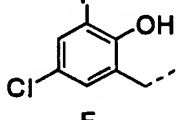
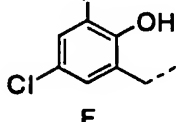
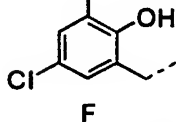
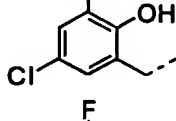
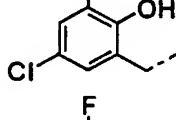
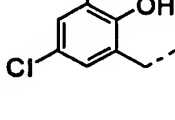
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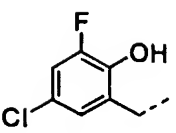
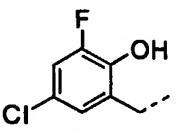
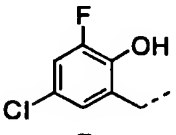
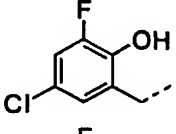
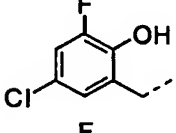

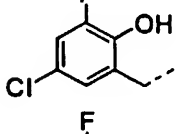
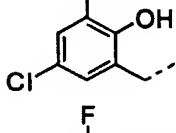
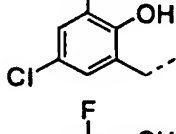
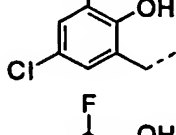
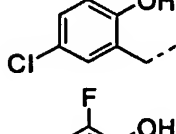
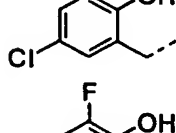
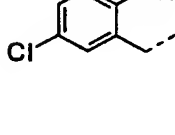
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646		H	H	H	SO <sub>2</sub> Me	F	H
647		H	H	SO <sub>2</sub> NMe <sub>2</sub>	H	H	H
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649		H	H	H	H	SO <sub>2</sub> NMe <sub>2</sub>	H
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651		H	H	H	SO <sub>2</sub> Et <sub>2</sub>	H	H
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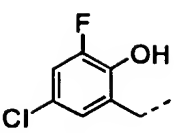
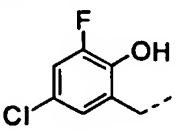
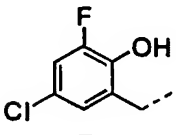
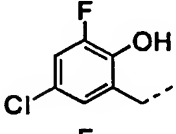
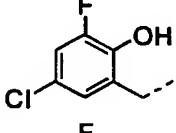

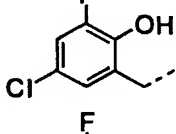
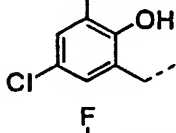
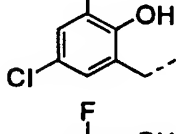
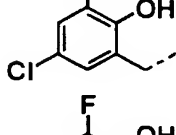
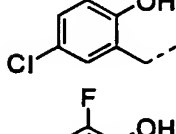
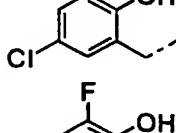
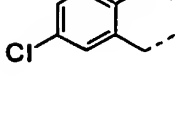
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661		H	H	NHCOEt	H	H	H
662		H	H	H	NHCOEt	H	H
663		H	H	H		NHCOEt	H
664		H	H	NHCOiPr	H	H	H
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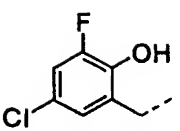
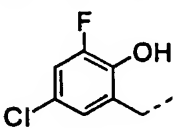
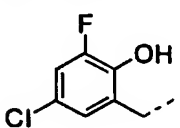
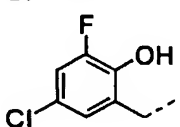
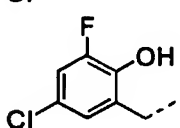
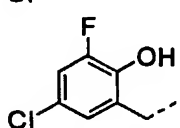
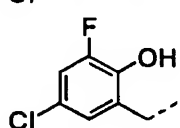
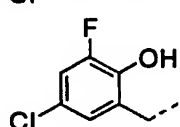
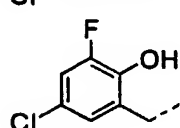
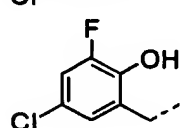
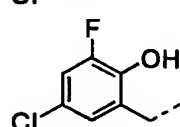
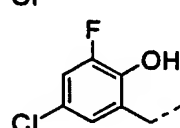
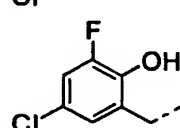
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674		H	H	Me	H	H	F
675		H	H	F	H	Me	H
676		H	H	F	H	H	Me
677		H	H	Me	H	H	Me
678		H	H	H	OMe	Me	H
679		H	H	H	OH	Me	H
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682		H	H	H	H	NH2	H
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687		H	H	H	iPr	H	H
688		H	H	H	H	iPr	H
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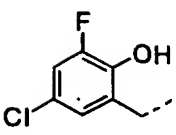
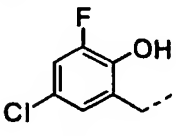
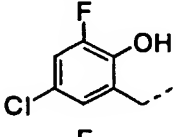
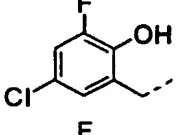

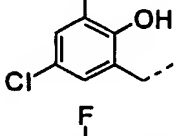
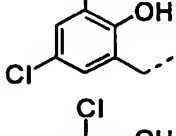
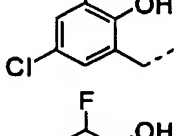
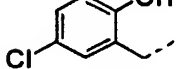
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699		H	H	H	OPh	H	H
700		H	H	H	H	OPh	H
701		H	H	SO2Me	H	H	H
702		H	H	H	SO2Me	H	H
703		H	H	H	H	SO2Me	H
704		H	H	SO2Et	H	H	H
705		H	H	H	SO2Et	H	H
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707		H	H	SO2iPr	H	H	H

708		H	H	H	SO2iPr	H	H
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710		H	H	SO2Ph	H	H	H
711		H	H	H	SO2Ph	H	H
712		H	H	H	H	SO2Ph	H
713		H	H	SO2Me	Me	H	H
714		H	H	SO2Me	H	Me	H
715		H	H	Me	SO2Me	H	H
716		H	H	H	SO2Me	Me	H
717		H	H	SO2Me	F	H	H
718		H	H	SO2Me	H	F	H
719		H	H	F	SO2Me	H	H
720		H	H	H	SO2Me	F	H

721		H	H	SO <sub>2</sub> NMe <sub>2</sub>	H	H	H
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723		H	H	H	H	SO <sub>2</sub> NMe <sub>2</sub>	H
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726		H	H	H	H	SO <sub>2</sub> Et <sub>2</sub>	H
727		H	H	SO <sub>2</sub> NMe <sub>2</sub>	Me	H	H
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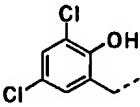
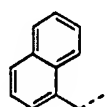
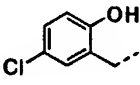
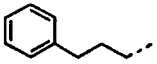
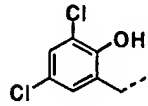
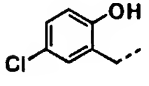
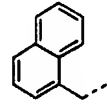
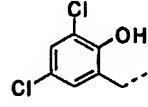
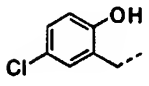
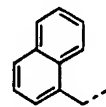


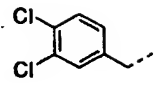
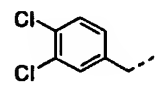
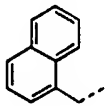
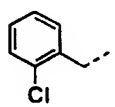
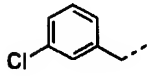
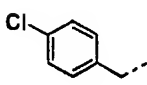
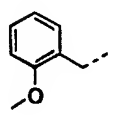
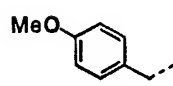
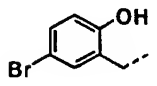
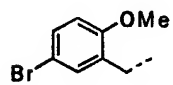
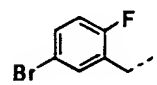
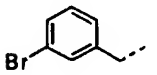
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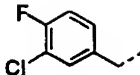
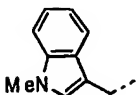
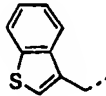
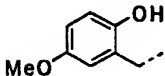
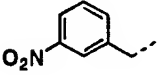
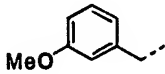
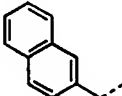

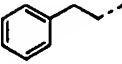
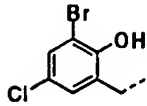
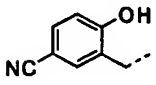
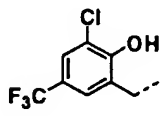
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736		H	H	H	NHCOEt	H	H
737		H	H	H	H	NHCOEt	H
738		H	H	NHCOiPr	H	H	H
739		H	H	H	NHCOiPr	H	H
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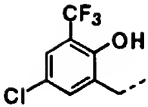
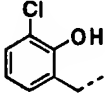
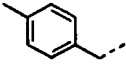
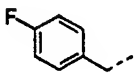
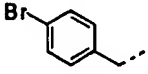
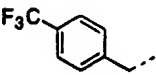
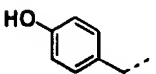
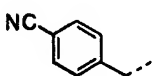
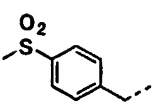
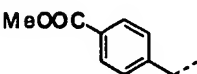
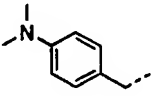
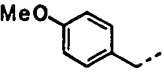
$$X = -SO_2-, q = 0, r = 0, Y = -(R_4)C=C(R_5)-$$

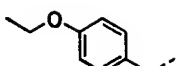
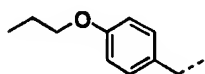
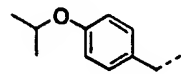
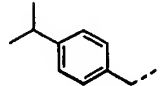
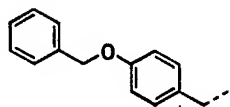
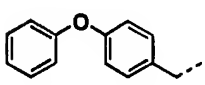
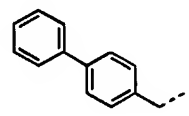
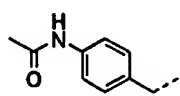
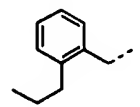
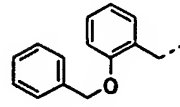
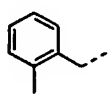
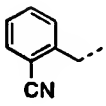
表 3



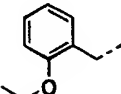
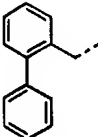
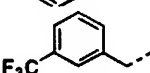
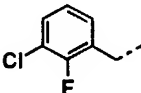
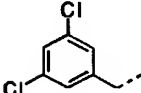
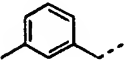
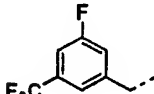
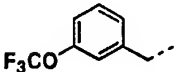
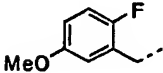
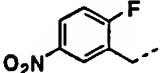
compnd NO.3—	R1-(CH <sub>2</sub> ) <sub>p</sub> —	R2	R3	R4	R5	R6	R7
1		H	H	H	H	H	H
2		H	H	H	H	H	H
3		H	H	H	H	H	H
4		H	H	H	H	H	H
5		H	H	H	Me	H	H
6		H	H	H	Me	H	H
7		H	H	H	Me	H	H
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9		H	H	H	F	H	H
10		H	H	H	F	H	H

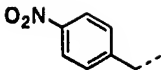
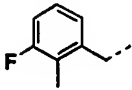
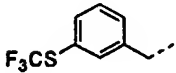
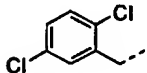
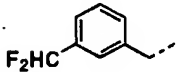
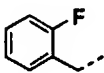
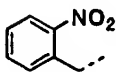
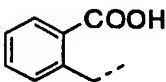
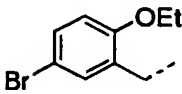
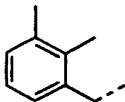
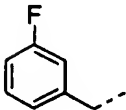
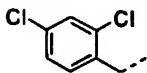
11		H	H	H	H	H	H
12		H	H	H	Cl	H	H
13		H	H	H	Cl	H	H
14		H	H	H	H	H	H
15		H	H	H	H	H	H
16		H	H	H	H	H	H
17		H	H	H	H	H	H
18		H	H	H	H	H	H
19		H	H	H	H	H	H
20		H	H	H	H	H	H
21		H	H	H	H	H	H
22		H	H	H	H	H	H

23		H	H	H	H	H	H
24		H	H	H	H	H	H
25		H	H	H	H	H	H
26		H	H	H	H	H	H
27		H	H	H	H	H	H
28		H	H	H	H	H	H
29		H	H	H	H	H	H
30		H	H	H	H	H	H
31		H	H	H	H	H	H
32		H	H	H	H	H	H
33		H	H	H	H	H	H
34		H	H	H	H	H	H

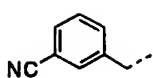
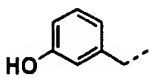
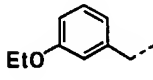
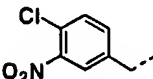
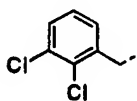
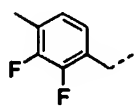
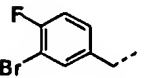
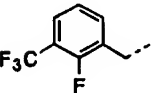
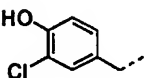
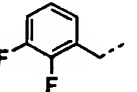
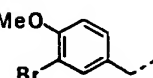
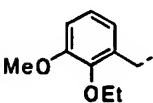
35		H	H	H	H	H	H
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38		H	H	H	H	H	H
39		H	H	H	H	H	H
40		H	H	H	H	H	H
41		H	H	H	H	H	H
42		H	H	H	H	H	H
43		H	H	H	H	H	H
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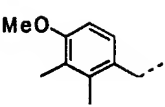
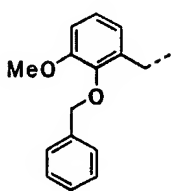
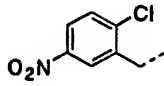
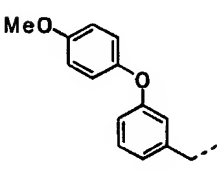
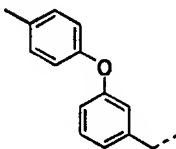
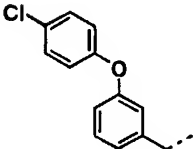
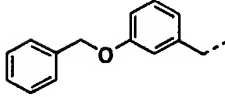
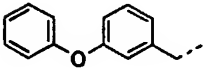
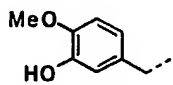
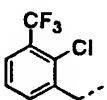
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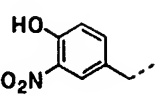
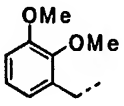
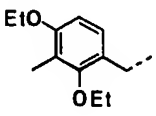
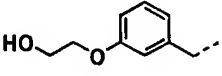
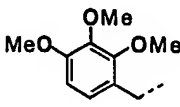
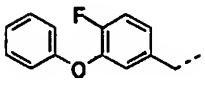
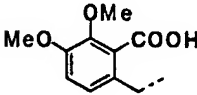
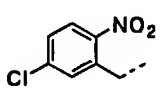
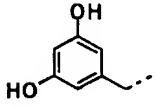
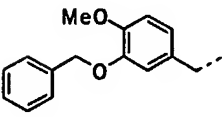
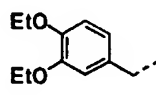
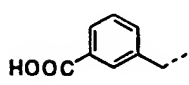
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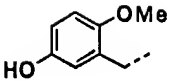
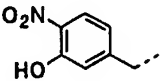
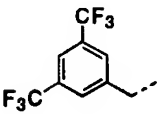
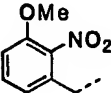
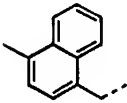
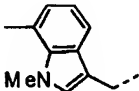
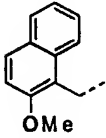
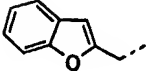
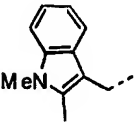
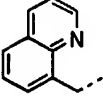
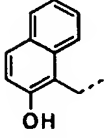
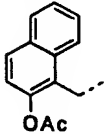
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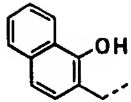
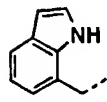
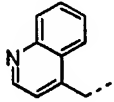
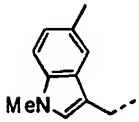
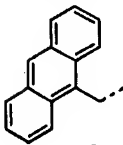
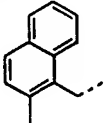
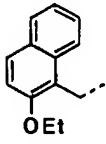
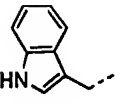
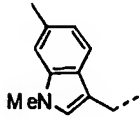
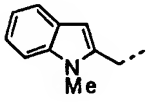
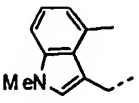
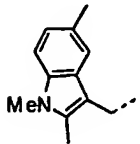


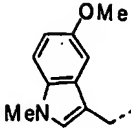
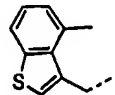
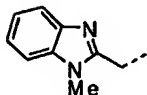
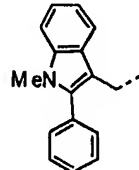
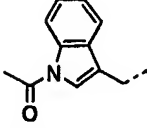
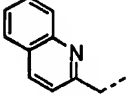
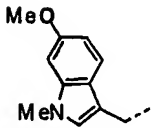
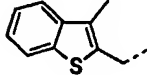
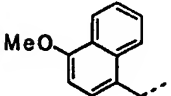
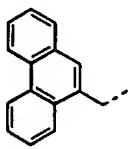
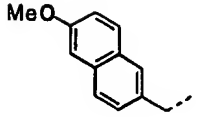
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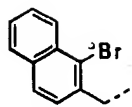
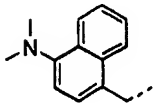
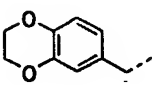
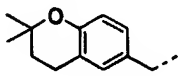
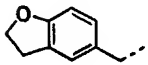
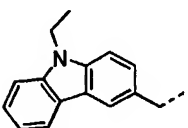
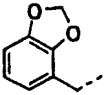
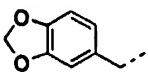
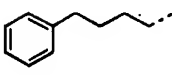
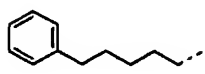

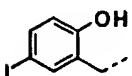
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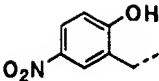
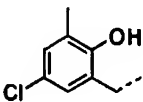
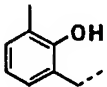
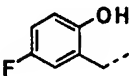
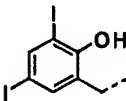
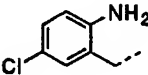
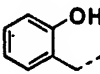
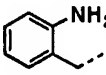
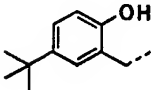
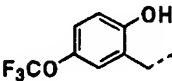
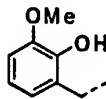
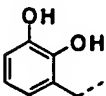
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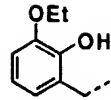
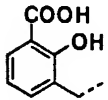
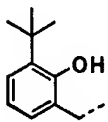
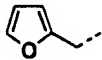



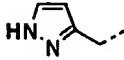
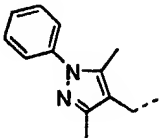
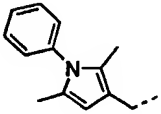
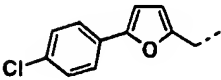

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



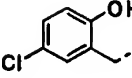
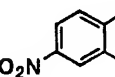
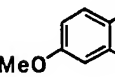

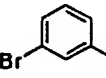
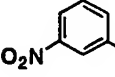
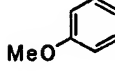
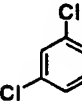
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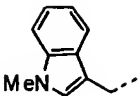
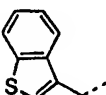
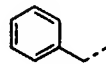
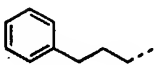
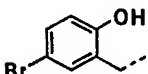
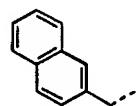
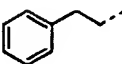
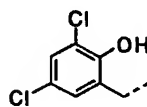
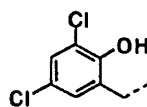
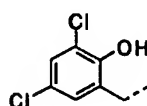
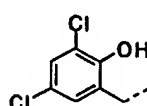
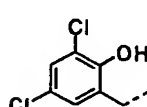
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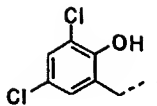
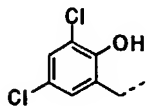
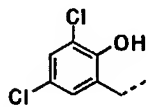
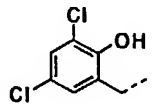
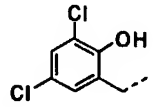
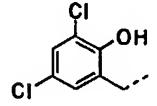
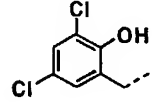
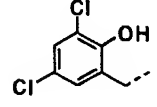
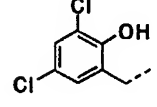
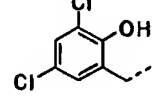
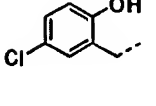
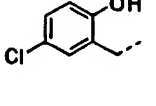


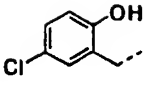
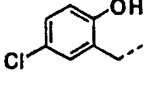
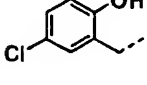
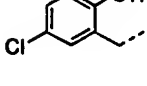
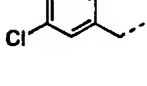
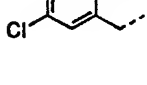
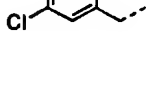
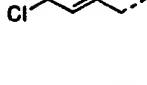


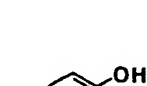

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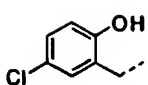
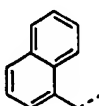
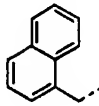
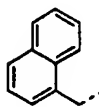
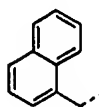
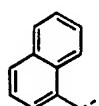
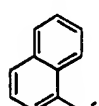
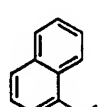
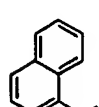
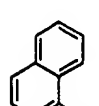
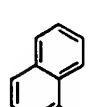
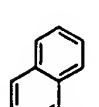
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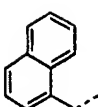
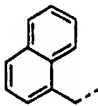
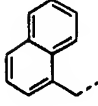
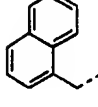
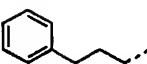

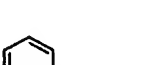
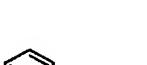



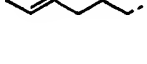
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229		H	H	COOMe	H	H	H
230		H	H	H	CF3	H	H
231		H	H	H	OH	H	H
232		H	H	H	NO2	H	H
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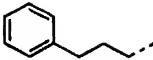
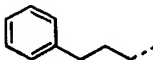
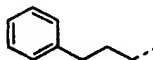
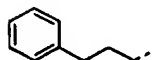
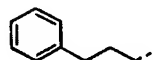
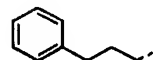
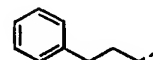
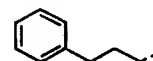
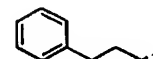
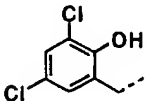
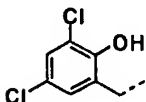
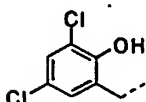
200

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238		H	H	H	OMe	H	H
239		H	H	H	COOMe	H	H
240		H	H	H	H	Cl	H
241		H	H	H	H	COOMe	H
242		H	H	H	H	H	Cl
243		H	H	H	OCF3	H	H
244		H	H	COOMe	H	H	H
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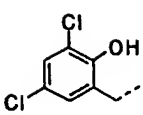
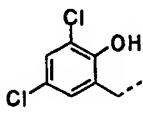
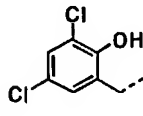
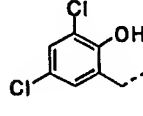
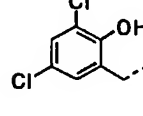
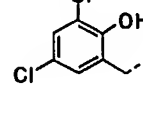
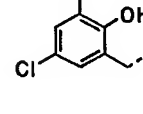
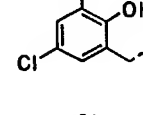
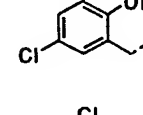
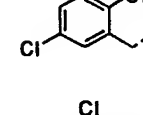
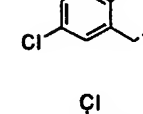
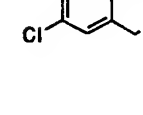
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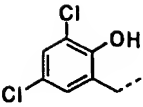
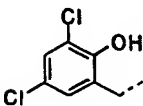
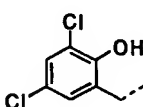
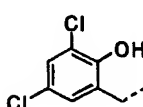
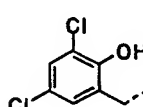
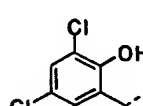
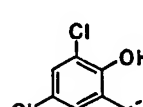
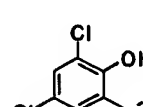
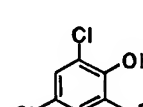
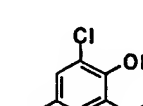
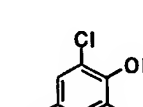
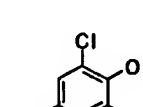
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253		H	H	H	OMe	H	H
254		H	H	H	COOMe	H	H
255		H	H	H	H	Cl	H
256		H	H	H	H	COOMe	H
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202

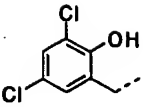
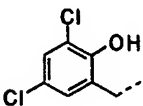
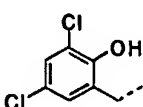
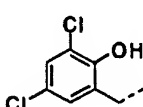
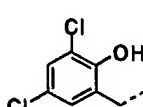
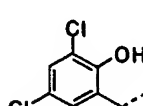
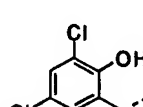
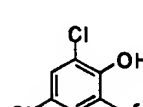
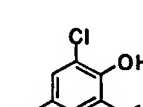
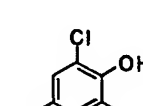
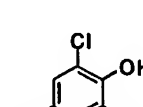
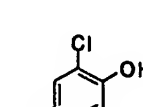
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263		H	H	H	OH	H	H
264		H	H	H	NO2	H	H
265		H	H	H	F	F	H
266		H	H	F	H	H	H
267		H	H	Me	H	H	H
268		H	H	H	CN	H	H
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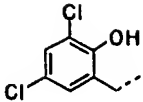
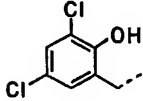
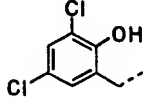
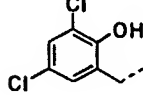
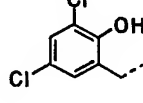
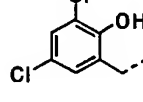
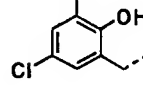
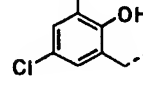
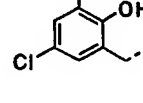
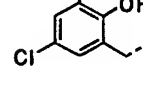
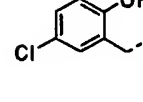
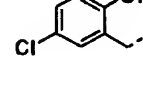


272		H	H	H	H	Me	H
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275		H	H	H	H	OMe	H
276		H	H	H	H	H	OMe
277		H	H	CF3	H	H	H
278		H	H	H	H	CF3	H
279		H	H	H	H	H	CF3
280		H	H	OH	H	H	H
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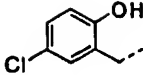
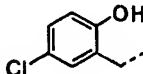
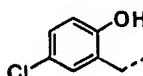
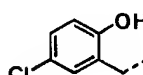
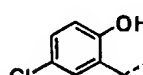
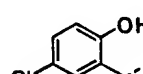
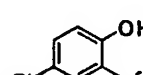
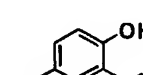
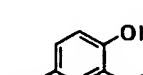
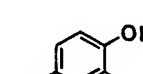
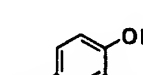
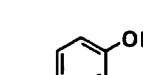
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286		H	H	NO2	H	H	H
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288		H	H	H	H	H	NO2
289		H	H	CN	H	H	H
290		H	H	H	H	CN	H
291		H	H	H	H	H	CN
292		H	H	Br	H	H	H
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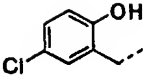
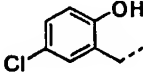
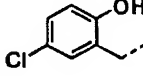
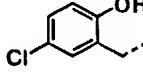
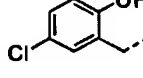
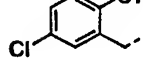
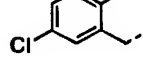
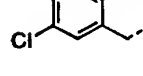
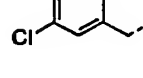
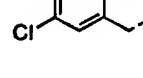
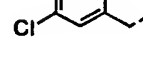
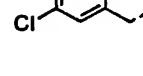
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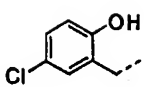
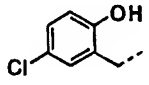
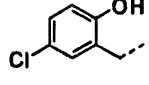
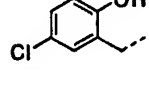
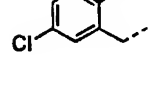
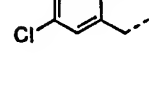
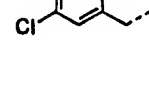
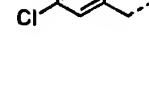
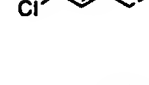
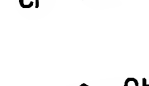


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301		H	H	H	NHCOMe	H	H
302		H	H	H	H	NHCOMe	H
303		H	H	H	H	H	NHCOMe
304		H	H	SO2NH2	H	H	H
305		H	H	H	SO2NH2	H	H
306		H	H	H	H	SO2NH2	H
307		H	H	H	H	H	SO2NH2

308		H	H	Me	Me	H	H
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310		H	H	H	Me	Me	H
311		H	H	F	F	H	H
312		H	H	F	H	F	H
313		H	H	H	F	F	H
314		H	H	Cl	Cl	H	H
315		H	H	Cl	H	Cl	H
316		H	H	H	Cl	Cl	H
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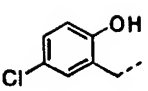
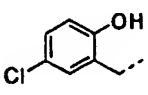
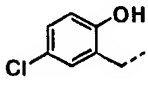
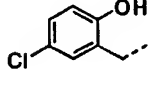
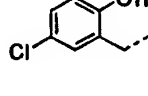
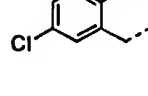
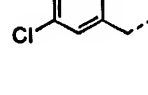
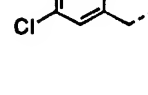
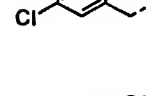
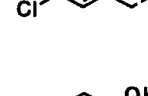
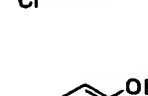

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325		H	H	Cl	Me	H	H
326		H	H	Cl	F	H	H
327		H	H	Cl	OH	H	H
328		H	H	Cl	OMe	H	H
329		H	H	H	H	H	COOMe
330		H	H	H	H	F	H
331		H	H	H	H	H	F

332		H	H	H	H	Me	H
333		H	H	H	H	H	Me
334		H	H	OMe	H	H	H
335		H	H	H	H	OMe	H
336		H	H	H	H	H	OMe
337		H	H	CF3	H	H	H
338		H	H	H	H	CF3	H
339		H	H	H	H	H	CF3
340		H	H	OH	H	H	H
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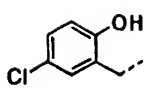
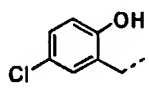
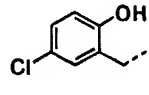
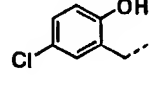
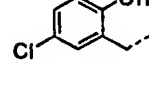
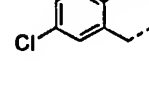
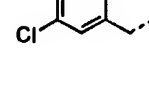
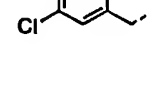
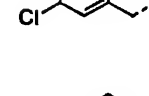
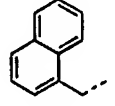
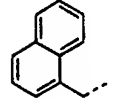
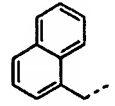
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349		H	H	CN	H	H	H
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351		H	H	H	H	H	CN
352		H	H	Br	H	H	H
353		H	H	H	Br	H	H
354		H	H	H	H	Br	H
355		H	H	H	H	H	Br

356		H	H	COOH	H	H	H
357		H	H	H	COOH	H	H
358		H	H	H	H	COOH	H
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360		H	H	NHCOMe	H	H	H
361		H	H	H	NHCOMe	H	H
362		H	H	H	H	NHCOMe	H
363		H	H	H	H	H	NHCOMe
364		H	H	SO2NH2	H	H	H
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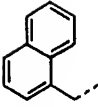
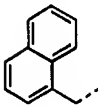
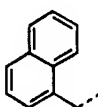
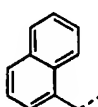
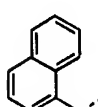
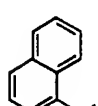
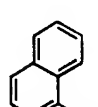
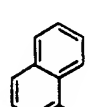
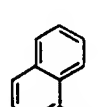
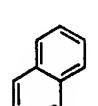
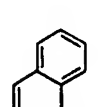
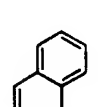


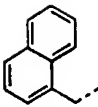
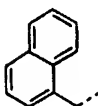
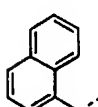
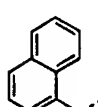
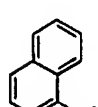
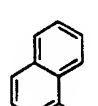
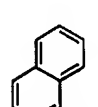
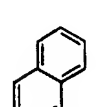
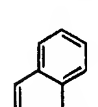
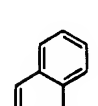
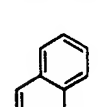
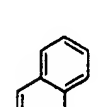
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212

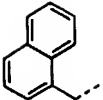
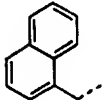
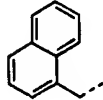
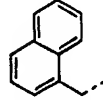
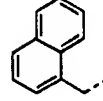
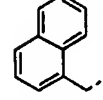
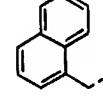
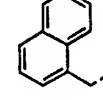
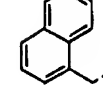
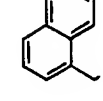
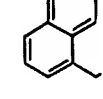
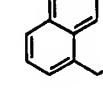
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384		H	H	F	OMe	H	H
385		H	H	Cl	Me	H	H
386		H	H	Cl	F	H	H
387		H	H	Cl	OH	H	H
388		H	H	Cl	OMe	H	H
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213

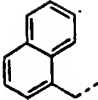
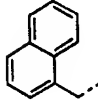
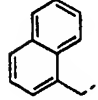
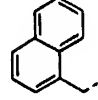
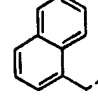
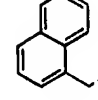
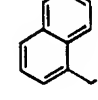
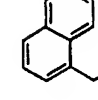
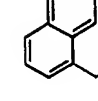
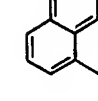

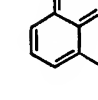
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396		H	H	H	H	H	OMe
397		H	H	CF3	H	H	H
398		H	H	H	H	CF3	H
399		H	H	H	H	H	CF3
400		H	H	OH	H	H	H
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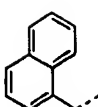
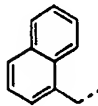
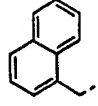
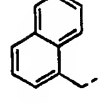
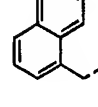
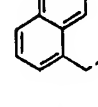
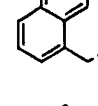
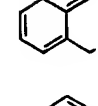
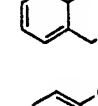
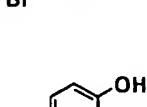
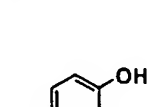

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406		H	H	NO2	H	H	H
407		H	H	H	H	NO2	H
408		H	H	H	H	H	NO2
409		H	H	CN	H	H	H
410		H	H	H	H	CN	H
411		H	H	H	H	H	CN
412		H	H	Br	H	H	H
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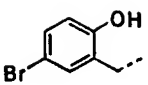
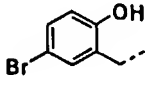
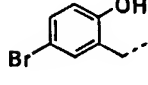
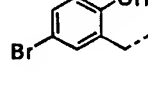
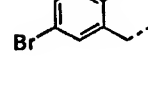
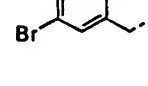
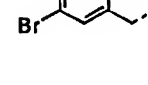
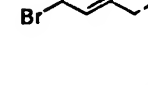
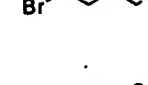
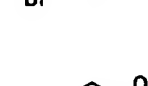


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416		H	H	COOH	H	H	H
417		H	H	H	COOH	H	H
418		H	H	H	H	COOH	H
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420		H	H	NHCOMe	H	H	H
421		H	H	H	NHCOMe	H	H
422		H	H	H	H	NHCOMe	H
423		H	H	H	H	H	NHCOMe
424		H	H	SO <sub>2</sub> NH <sub>2</sub>	H	H	H
425		H	H	H	SO <sub>2</sub> NH <sub>2</sub>	H	H
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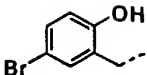
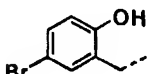
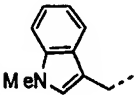
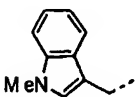
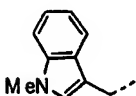
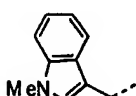
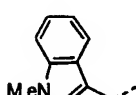
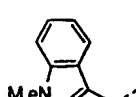
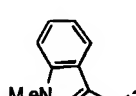
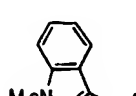
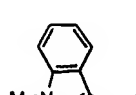
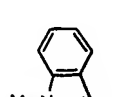
216

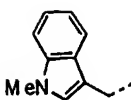
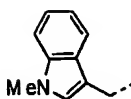
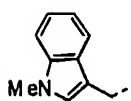
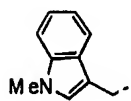
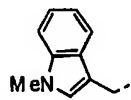
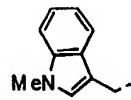
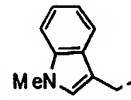
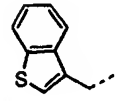
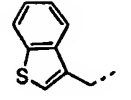
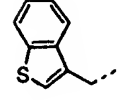
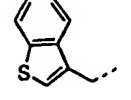
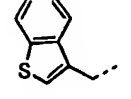
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433		H	H	H	F	F	H
434		H	H	Cl	Cl	H	H
435		H	H	Cl	H	Cl	H
436		H	H	H	Cl	Cl	H
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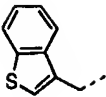
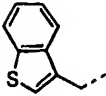
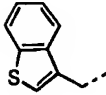
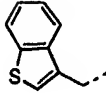
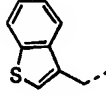
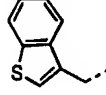
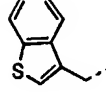
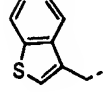
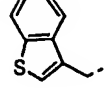
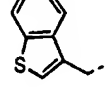
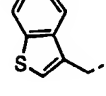
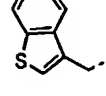
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444		H	H	F	OMe	H	H
445		H	H	Cl	Me	H	H
446		H	H	Cl	F	H	H
447		H	H	Cl	OH	H	H
448		H	H	Cl	OMe	H	H
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450		H	H	H	OMe	H	H
451		H	H	H	COOMe	H	H

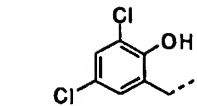
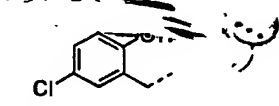
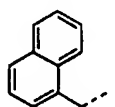
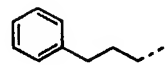
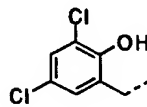
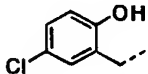
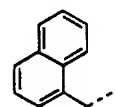
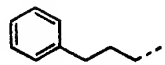
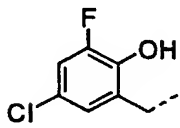
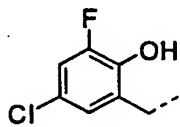
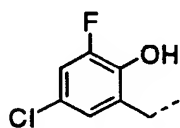
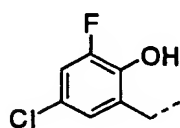
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456		H	H	COOMe	H	H	H
457		H	H	H	CF3	H	H
458		H	H	H	Me	H	H
459		H	H	H	F	H	H
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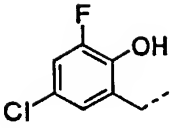
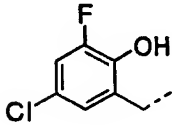
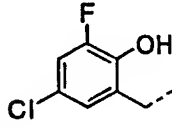
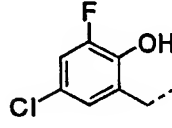
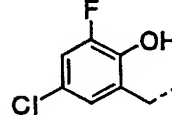
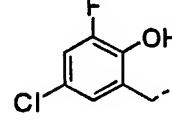
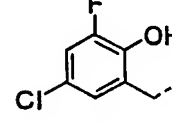
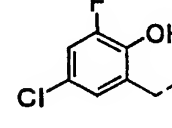
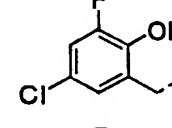
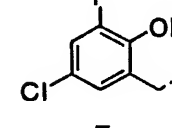
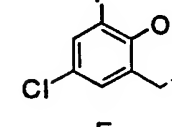
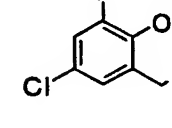


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471		H	H	H	H	H	Cl
472		H	H	H	OCF3	H	H
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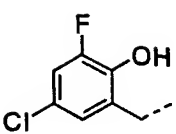
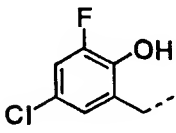
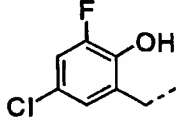
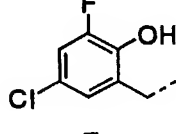
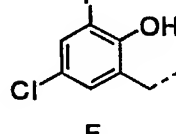
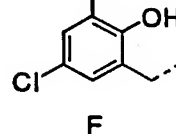
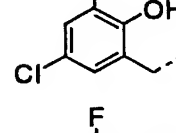
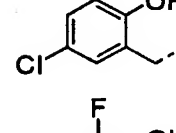
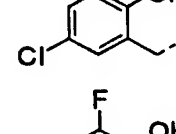

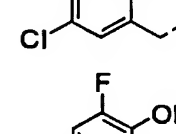
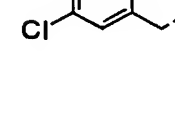
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482		H	H	H	CN	H	H
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484		H	H	H	OMe	H	H
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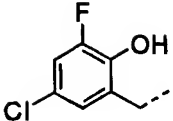
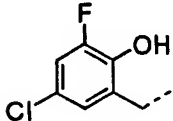
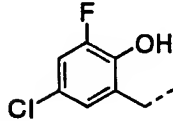
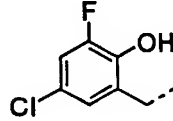
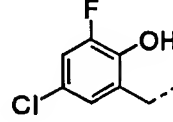
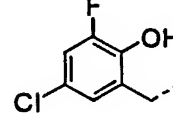
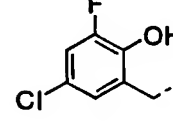
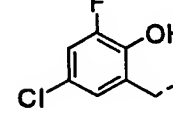
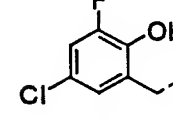
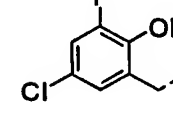
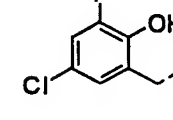
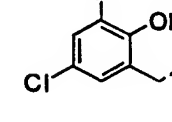
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493		H	H	H	F	H	H
494		H	H	H	OH	H	H
495		H	H	H	NO2	H	H
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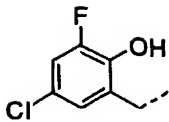
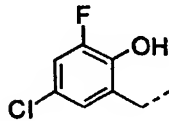
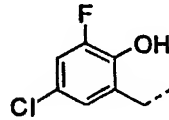
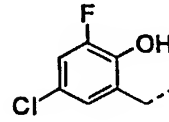
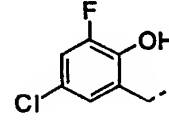
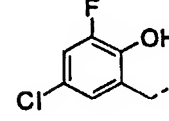
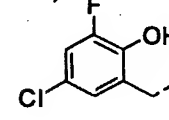
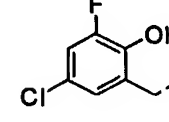
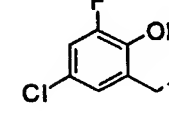
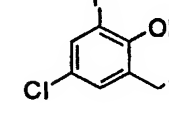
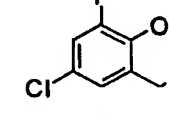
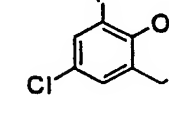
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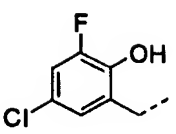
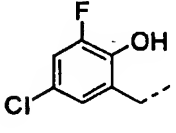
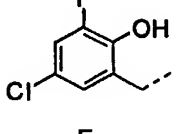
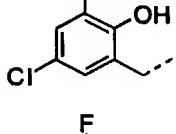
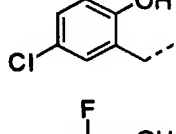
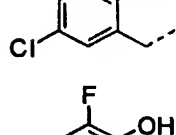
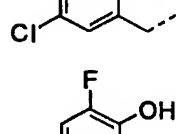
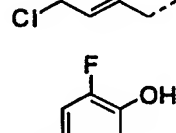
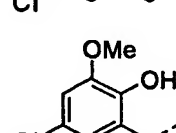
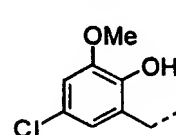
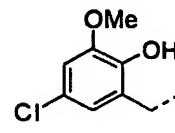

224

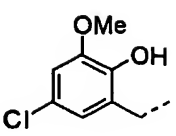
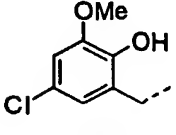
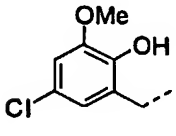
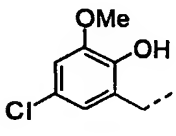
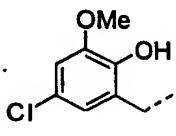
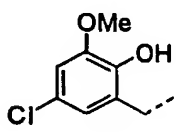
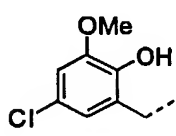
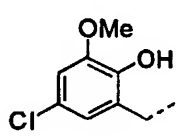
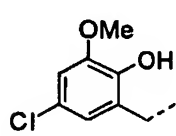
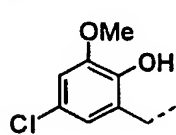
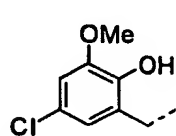
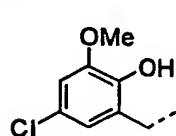
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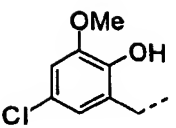
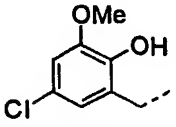
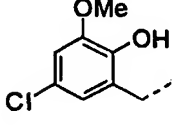
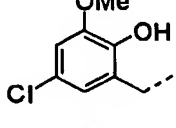
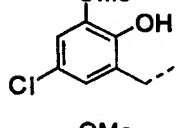
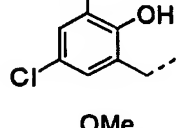
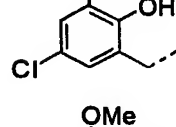
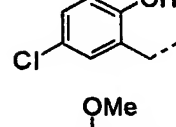
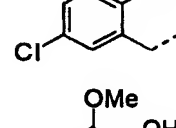
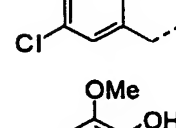
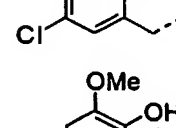
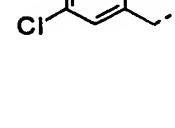
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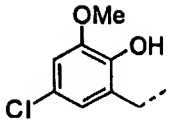
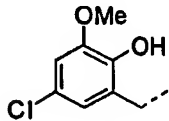
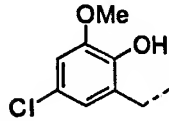
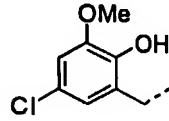
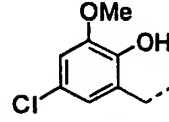
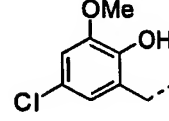
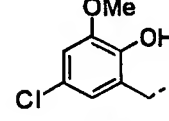
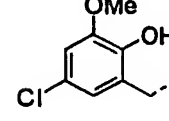
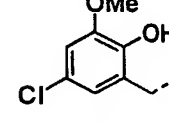
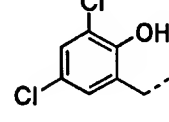
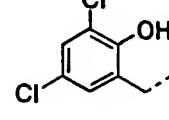
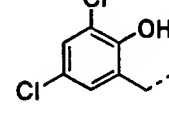


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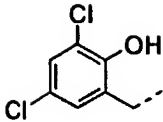
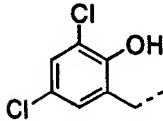
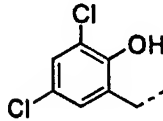
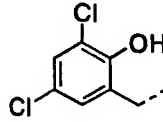
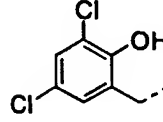
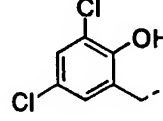
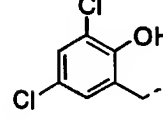
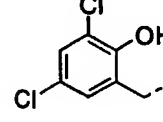
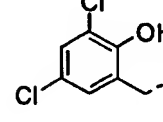
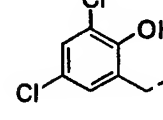
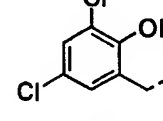
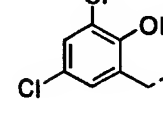
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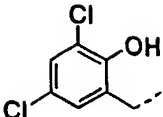
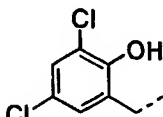
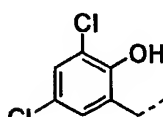
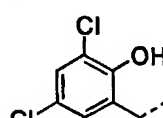
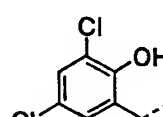
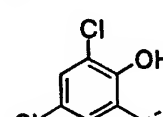
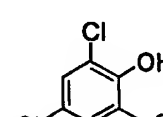
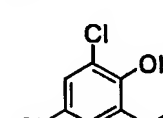
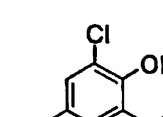
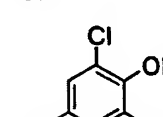
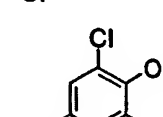
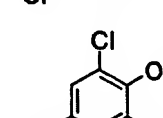
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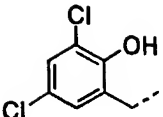
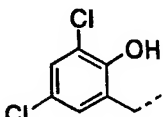
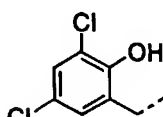
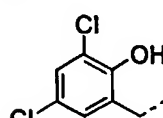
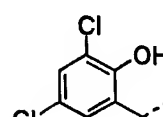
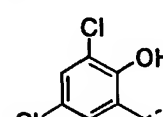
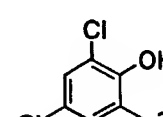
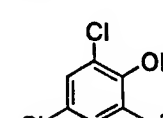
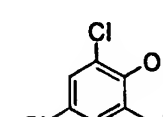
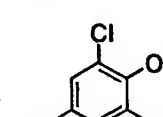
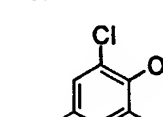
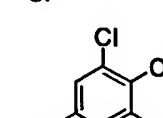
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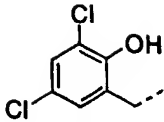
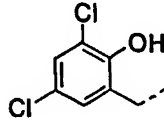
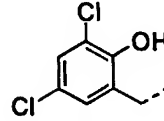
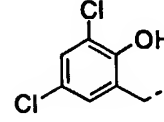
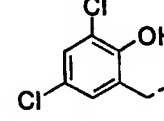
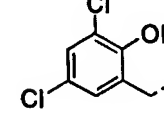
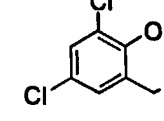
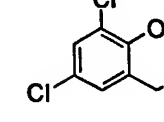
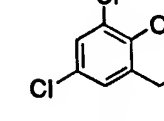
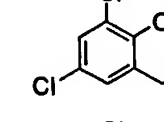
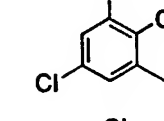
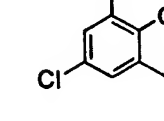
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616		H	H	H	OMe	Me	H
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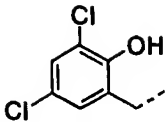
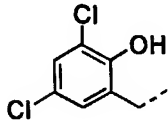
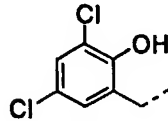
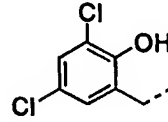
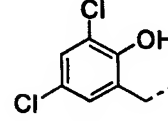
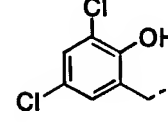
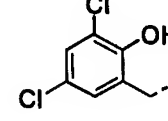
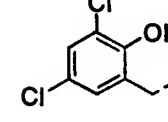
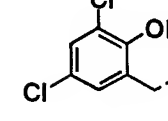
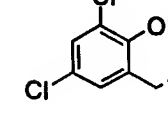
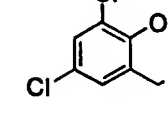
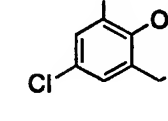
232

620		H	H	H	H	NH2	H
621		H	H	Et	H	H	H
622		H	H	H	Et	H	H
623		H	H	H	H	Et	H
624		H	H	iPr	H	H	H
625		H	H	H	iPr	H	H
626		H	H	H	H	iPr	H
627		H	H	Ph	H	H	H
628		H	H	H	Ph	H	H
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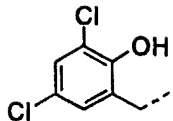
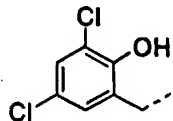
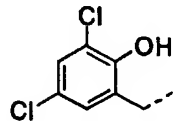
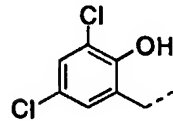
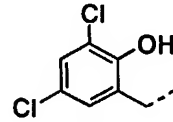
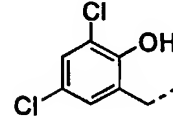
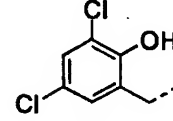
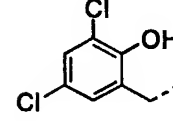
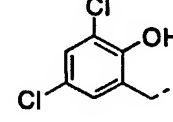
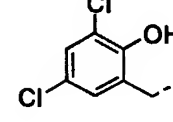
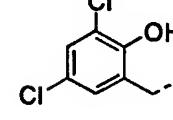
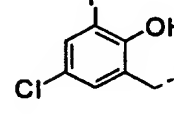
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633		H	H	OiPr	H	H	H
634		H	H	H	OiPr	H	H
635		H	H	H	H	OiPr	H
636		H	H	OPh	H	H	H
637		H	H	H	OPh	H	H
638		H	H	H	H	OPh	H
639		H	H	SO2Me	H	H	H
640		H	H	H	SO2Me	H	H
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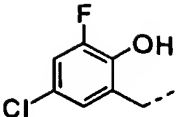
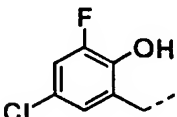
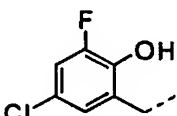
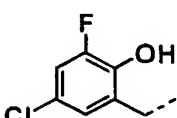
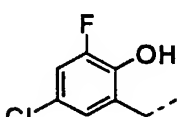
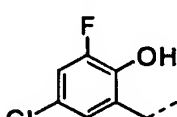
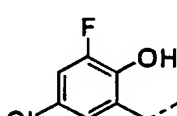
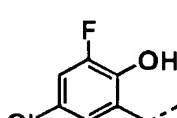
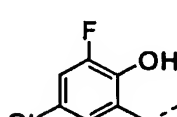
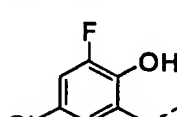
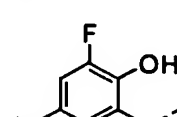
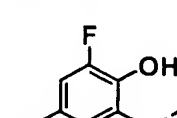
644		H	H	H	H	SO2Et	H
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648		H	H	SO2Ph	H	H	H
649		H	H	H	SO2Ph	H	H
650		H	H	H	H	SO2Ph	H
651		H	H	SO2Me	Me	H	H
652		H	H	SO2Me	H	Me	H
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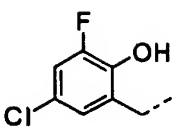
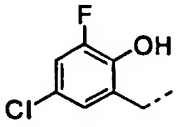
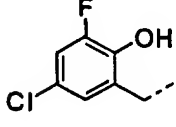
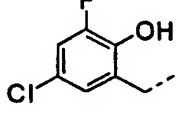
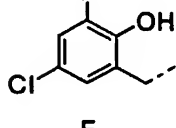
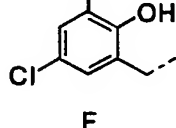
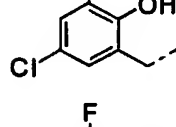
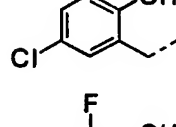
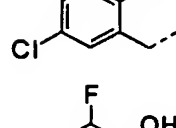
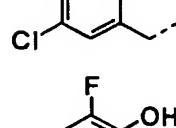
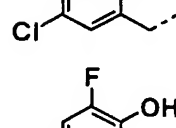
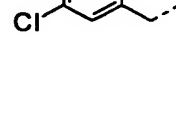


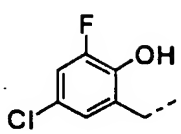
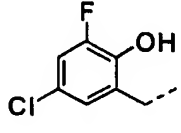
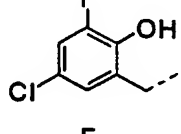
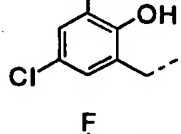
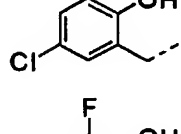
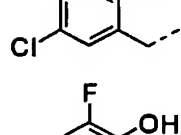
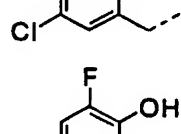
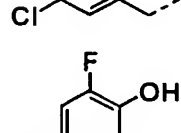
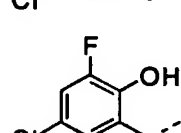
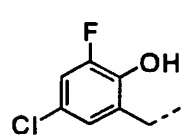
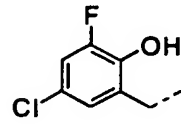

656		H	H	SO <sub>2</sub> Me	H	F	H
657		H	H	F	SO <sub>2</sub> Me	H	H
658		H	H	H	SO <sub>2</sub> Me	F	H
659		H	H	SO <sub>2</sub> NMe <sub>2</sub>	H	H	H
660		H	H	H	SO <sub>2</sub> NMe <sub>2</sub>	H	H
661		H	H	H	H	SO <sub>2</sub> NMe <sub>2</sub>	H
662		H	H	SO <sub>2</sub> Et <sub>2</sub>	H	H	H
663		H	H	H	SO <sub>2</sub> Et <sub>2</sub>	H	H
664		H	H	H	H	SO <sub>2</sub> Et <sub>2</sub>	H
665		H	H	SO <sub>2</sub> NMe <sub>2</sub>	Me	H	H
666		H	H	SO <sub>2</sub> NMe <sub>2</sub>	H	Me	H
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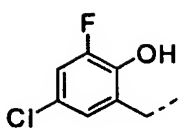
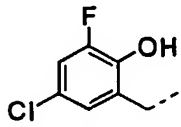
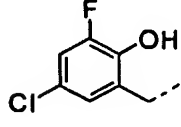
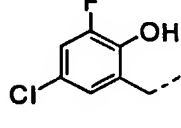
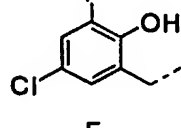
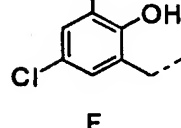
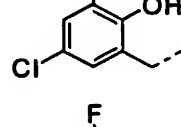
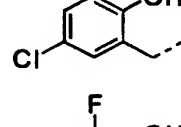
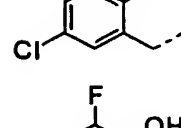
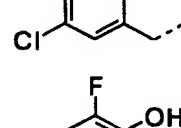
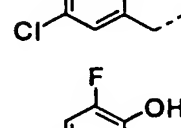
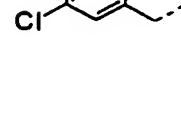
236

668		H	H	H	SO <sub>2</sub> NMe <sub>2</sub>	Me	H
669		H	H	SO <sub>2</sub> NMe <sub>2</sub>	F	H	H
670		H	H	SO <sub>2</sub> NMe <sub>2</sub>	H	F	H
671		H	H	F	SO <sub>2</sub> NMe <sub>2</sub>	H	H
672		H	H	H	SO <sub>2</sub> NMe <sub>2</sub>	F	H
673		H	H	NHCOEt	H	H	H
674		H	H	H	NHCOEt	H	H
675		H	H	H	H	NHCOEt	H
676		H	H	NHCOiPr	H	H	H
677		H	H	H	NHCOiPr	H	H
678		H	H	H	H	NHCOiPr	H
679		H	H	Me	CN	H	H

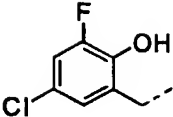
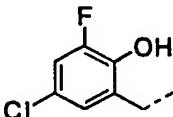
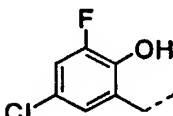
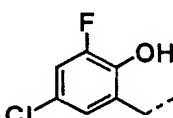
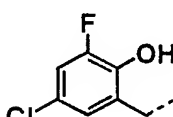
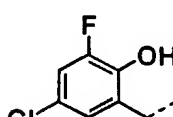
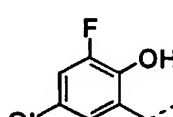
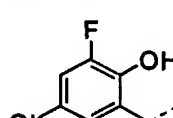
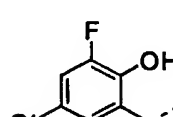
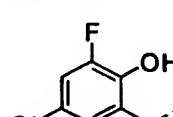
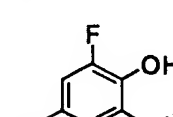
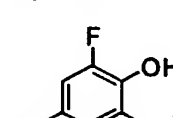
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683		H	H	H	Br	Me	H
684		H	H	H	Br	H	Me
685		H	H	Me	H	F	H
686		H	H	Me	H	H	F
687		H	H	F	H	Me	H
688		H	H	F	H	H	Me
689		H	H	Me	H	H	Me
690		H	H	H	OMe	Me	H
691		H	H	H	OH	Me	H

692		H	H	NH2	H	H	H
693		H	H	H	NH2	H	H
694		H	H	H	H	NH2	H
695		H	H	Et	H	H	H
696		H	H	H	Et	H	H
697		H	H	H	H	Et	H
698		H	H	iPr	H	H	H
699		H	H	H	iPr	H	H
700		H	H	H	H	iPr	H
701		H	H	Ph	H	H	H
702		H	H	H	Ph	H	H
703		H	H	H	H	Ph	H

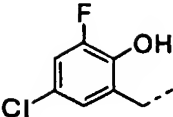
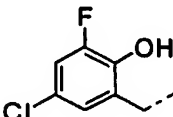
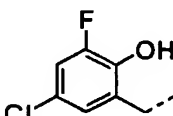
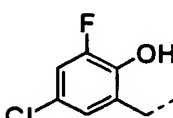
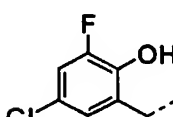
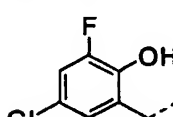
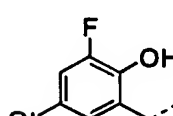
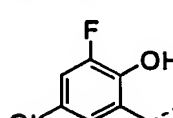
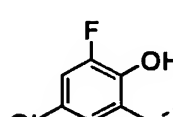
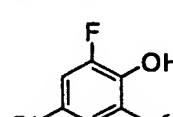
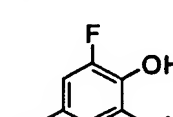
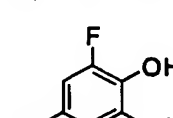
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705		H	H	H	OEt	H	H
706		H	H	H	H	OEt	H
707		H	H	OiPr	H	H	H
708		H	H	H	OiPr	H	H
709		H	H	H	H	OiPr	H
710		H	H	OPh	H	H	H
711		H	H	H	OPh	H	H
712		H	H	H	H	OPh	H
713		H	H	SO2Me	H	H	H
714		H	H	H	SO2Me	H	H
715		H	H	H	H	SO2Me	H

716		H	H	SO2Et	H	H	H
717		H	H	H	SO2Et	H	H
718		H	H	H	H	SO2Et	H
719		H	H	SO2iPr	H	H	H
720		H	H	H	SO2iPr	H	H
721		H	H	H	H	SO2iPr	H
722		H	H	SO2Ph	H	H	H
723		H	H	H	SO2Ph	H	H
724		H	H	H	H	SO2Ph	H
725		H	H	SO2Me	Me	H	H
726		H	H	SO2Me	H	Me	H
727		H	H	Me	SO2Me	H	H

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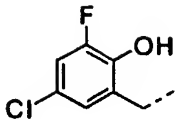
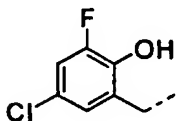
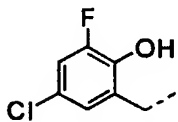
728		H	H	H	SO <sub>2</sub> Me	Me	H
729		H	H	SO <sub>2</sub> Me	F	H	H
730		H	H	SO <sub>2</sub> Me	H	F	H
731		H	H	F	SO <sub>2</sub> Me	H	H
732		H	H	H	SO <sub>2</sub> Me	F	H
733		H	H	SO <sub>2</sub> NMe <sub>2</sub>	H	H	H
734		H	H	H	SO <sub>2</sub> NMe <sub>2</sub>	H	H
735		H	H	H	H	SO <sub>2</sub> NMe <sub>2</sub>	H
736		H	H	SO <sub>2</sub> Et <sub>2</sub>	H	H	H
737		H	H	H	SO <sub>2</sub> Et <sub>2</sub>	H	H
738		H	H	H	H	SO <sub>2</sub> Et <sub>2</sub>	H
739		H	H	SO <sub>2</sub> NMe <sub>2</sub>	Me	H	H

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740		H	H	SO <sub>2</sub> NMe <sub>2</sub>	H	Me	H
741		H	H	Me	SO <sub>2</sub> NMe <sub>2</sub>	H	H
742		H	H	H	SO <sub>2</sub> NMe <sub>2</sub>	Me	H
743		H	H	SO <sub>2</sub> NMe <sub>2</sub>	F	H	H
744		H	H	SO <sub>2</sub> NMe <sub>2</sub>	H	F	H
745		H	H	F	SO <sub>2</sub> NMe <sub>2</sub>	H	H
746		H	H	H	SO <sub>2</sub> NMe <sub>2</sub>	F	H
747		H	H	NHCOEt	H	H	H
748		H	H	H	NHCOEt	H	H
749		H	H	H	H	NHCOEt	H
750		H	H	NHCOiPr	H	H	H
751		H	H	H	NHCOiPr	H	H

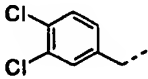
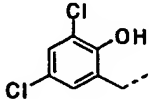
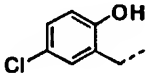
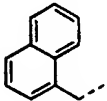
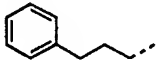
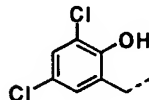
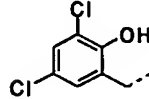
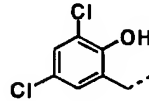
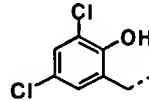
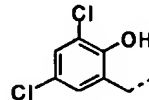
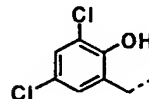


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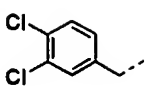
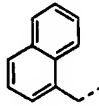
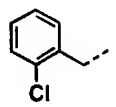
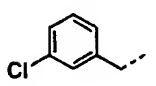
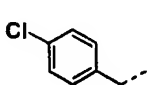
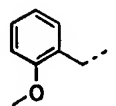
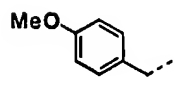
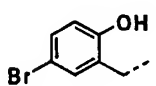
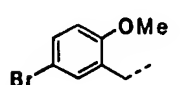
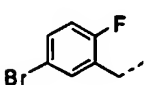
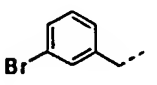
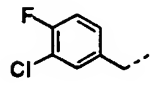
752		H	H	H	H	NHCOiPr	H
753		H	H	F	H	H	F
754		H	H	F	H	H	F

$$X = -CH_2-, q = 0, r = 0, Y = -(R_4)C=C(R_5)-$$

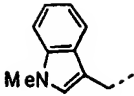
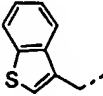
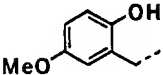
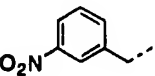
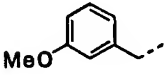
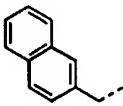
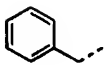
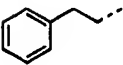
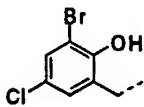
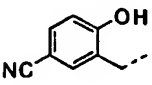
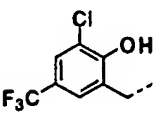
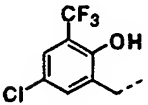
表 4

compnd NO.4—	R1-(CH <sub>2</sub> ) <sub>p</sub> —	R2	R3	R4	R5	R6	R7
1		H	H	H	H	H	H
2		H	H	H	H	H	H
3		H	H	H	H	H	H
4		H	H	H	H	H	H
5		H	H	H	H	H	H
6		H	H	H	OCF <sub>3</sub>	H	H
7		H	H	H	Cl	H	H
8		H	H	H	Me	H	H
9		H	H	H	F	H	H
10		H	H	Me	H	H	H
11		H	H	H	OH	H	H

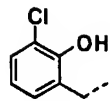
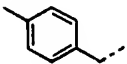
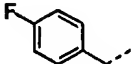
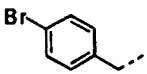
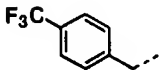
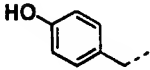
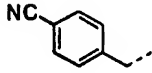
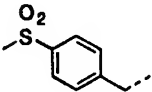
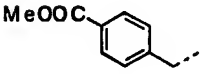
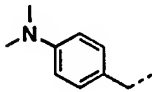
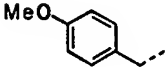
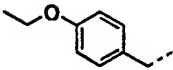
245

12		H	H	H	Cl	H	H
13		H	H	H	Cl	H	H
14		H	H	H	H	H	H
15		H	H	H	H	H	H
16		H	H	H	H	H	H
17		H	H	H	H	H	H
18		H	H	H	H	H	H
19		H	H	H	H	H	H
20		H	H	H	H	H	H
21		H	H	H	H	H	H
22		H	H	H	H	H	H
23		H	H	H	H	H	H

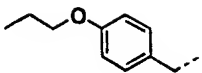
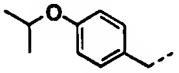
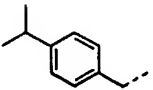
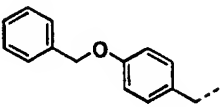
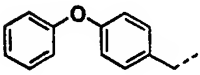
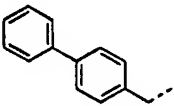
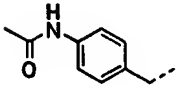
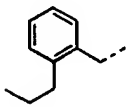
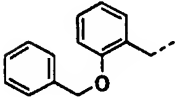
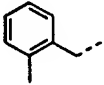
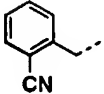
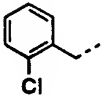
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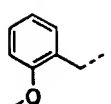
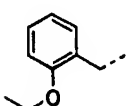
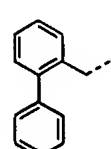
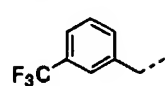
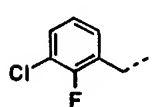
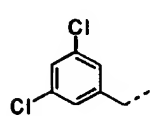
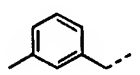
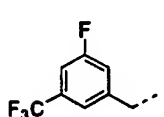
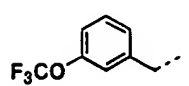
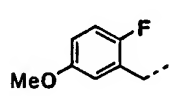
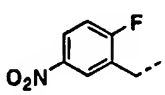
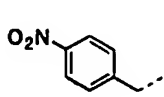
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32		H	H	H	H	H	H
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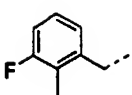
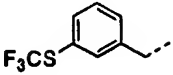
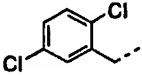
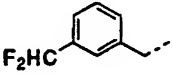
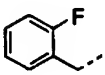
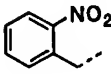
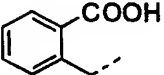
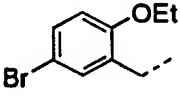
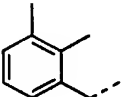
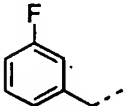
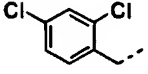
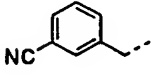
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248

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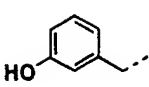
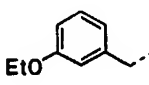
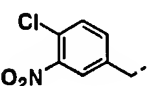
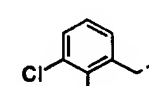
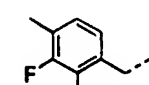
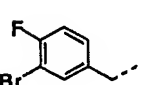
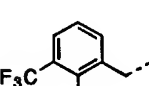
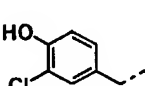
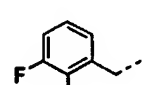
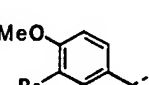
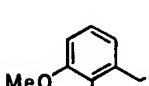
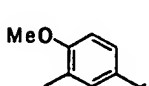
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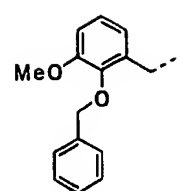
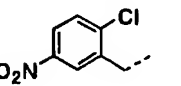
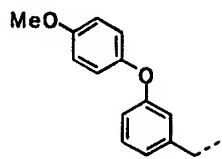
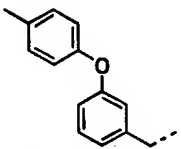
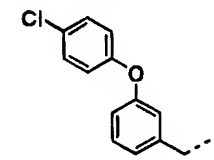
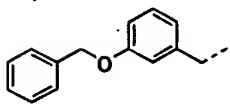
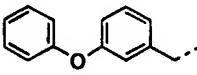
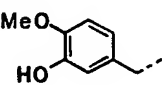
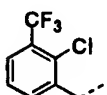
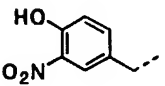
250

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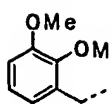
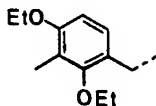
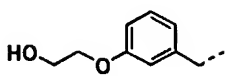
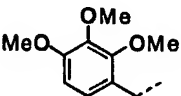
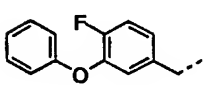
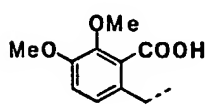
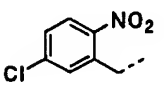
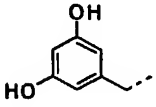
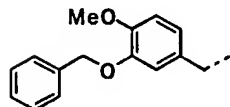
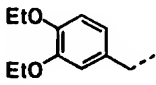
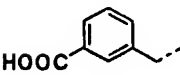
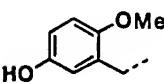


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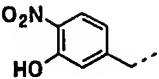
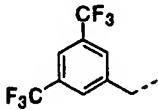
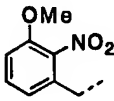
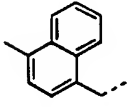
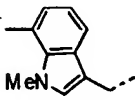
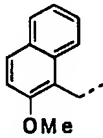
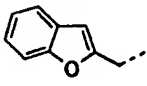
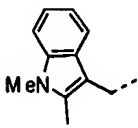
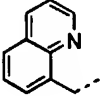
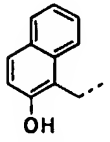
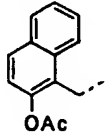
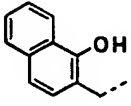
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96		H	H	H	H	H	H
97		H	H	H	H	H	H
98		H	H	H	H	H	H
99		H	H	H	H	H	H
100		H	H	H	H	H	H
101		H	H	H	H	H	H
102		H	H	H	H	H	H
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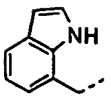
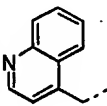
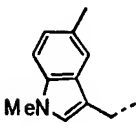
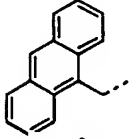
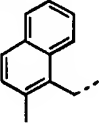
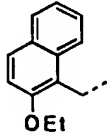
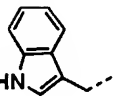
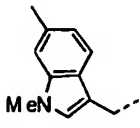
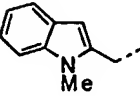
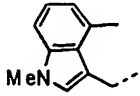
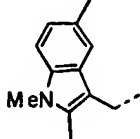
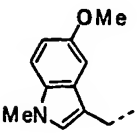
253

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111		H	H	H	H	H	H
112		H	H	H	H	H	H
113		H	H	H	H	H	H
114		H	H	H	H	H	H
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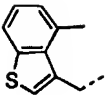
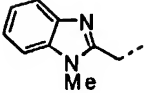
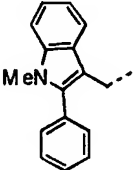
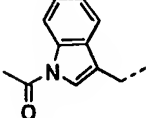
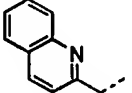
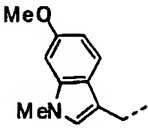
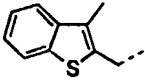
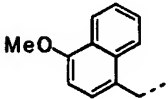
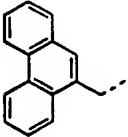
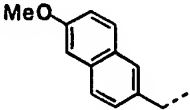
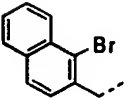
254

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121		H	H	H	H	H	H
122		H	H	H	H	H	H
123		H	H	H	H	H	H
124		H	H	H	H	H	H
125		H	H	H	H	H	H
126		H	H	H	H	H	H
127		H	H	H	H	H	H
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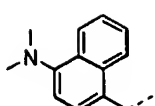
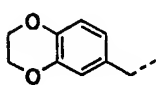
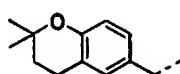
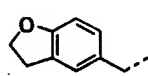
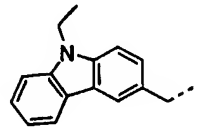
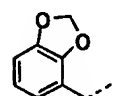
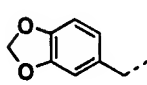
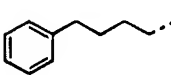
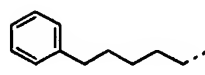
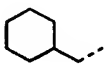
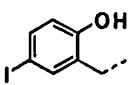
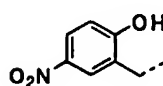
255

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135		H	H	H	H	H	H
136		H	H	H	H	H	H
137		H	H	H	H	H	H
138		H	H	H	H	H	H
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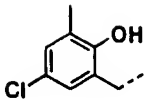
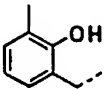
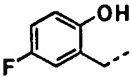
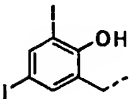
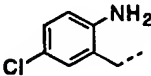
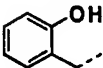
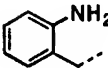
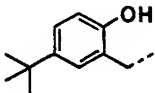
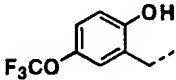
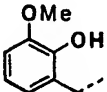
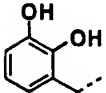
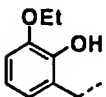
256

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146		H	H	H	H	H	H
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149		H	H	H	H	H	H
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257

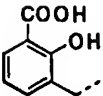
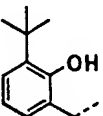
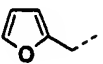
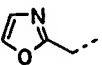
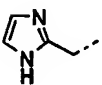
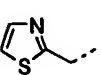
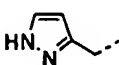
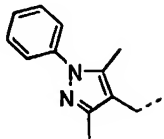
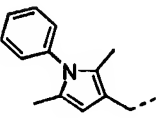
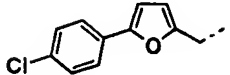
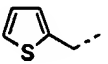

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258

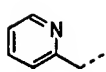
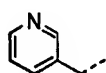
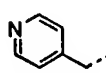
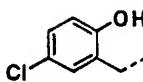
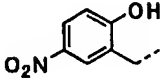
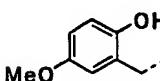
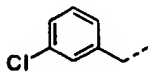
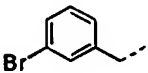
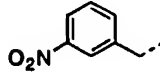
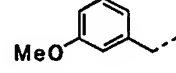
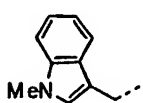
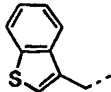
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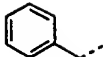
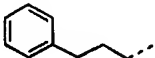
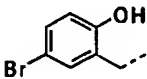
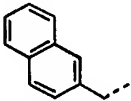
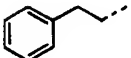
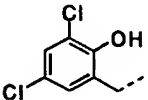
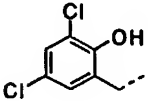
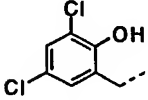
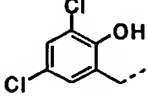
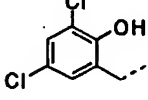
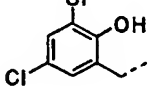
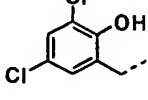
259

177		H	H	H	H	H	H
178		H	H	H	H	H	H
179		H	H	H	H	H	H
180		H	H	H	H	H	H
181		H	H	H	H	H	H
182		H	H	H	H	H	H
183		H	H	H	H	H	H
184		H	H	H	H	H	H
185		H	H	H	H	H	H
186		H	H	H	H	H	H
187		H	H	H	H	H	H
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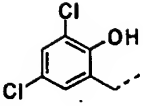
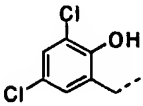
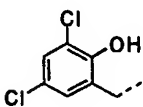
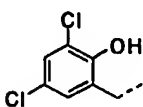
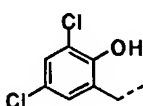
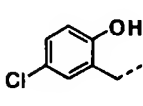
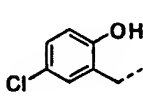
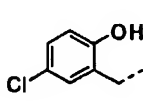
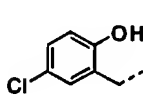
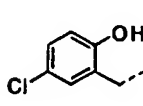
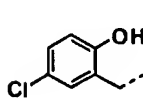
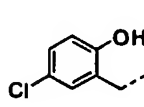
260

189		H	H	H	H	H	H
190		H	H	H	H	H	H
191		H	H	H	H	H	H
192		H	H	H	Cl	H	H
193		H	H	H	Cl	H	H
194		H	H	H	Cl	H	H
195		H	H	H	Cl	H	H
196		H	H	H	Cl	H	H
197		H	H	H	Cl	H	H
198		H	H	H	Cl	H	H
199		H	H	H	Cl	H	H
200		H	H	H	Cl	H	H

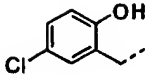
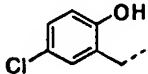
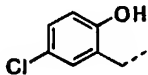
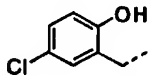
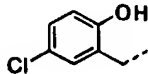
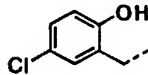
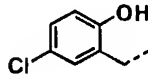
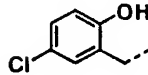
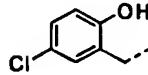
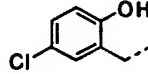
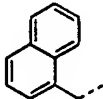
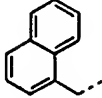
261

201		H	H	H	Cl	H	H
202		H	H	H	Cl	H	H
203		H	H	H	Cl	H	H
204		H	H	H	Cl	H	H
205		H	H	H	Cl	H	H
206		H	H	Cl	H	H	H
207		H	H	H	OMe	H	H
208		H	H	H	COOMe	H	H
209		H	H	H	H	Cl	H
210		H	H	H	H	COOMe	H
211		H	H	H	H	H	Cl
212		H	H	COOMe	H	H	H

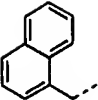
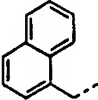
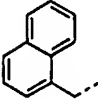
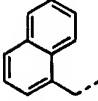
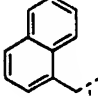
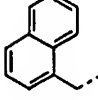

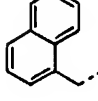
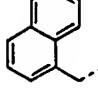

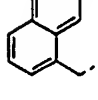
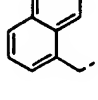
262

213		H	H	H	CF3	H	H
214		H	H	H	NO2	H	H
215		H	H	H	F	F	H
216		H	H	F	H	H	H
217		H	H	H	CN	H	H
218		H	H	Cl	H	H	H
219		H	H	H	OMe	H	H
220		H	H	H	COOMe	H	H
221		H	H	H	H	Cl	H
222		H	H	H	H	COOMe	H
223		H	H	H	H	H	Cl
224		H	H	H	OCF3	H	H

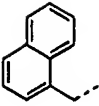
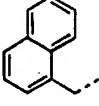
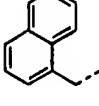
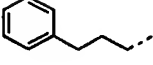
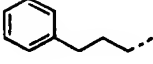
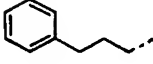
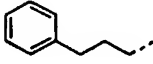
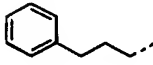
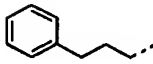
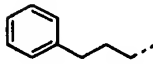
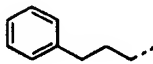
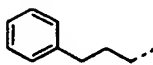
263

225		H	H	COOMe	H	H	H
226		H	H	H	CF3	H	H
227		H	H	H	Me	H	H
228		H	H	H	F	H	H
229		H	H	H	OH	H	H
230		H	H	H	NO2	H	H
231		H	H	H	F	F	H
232		H	H	F	H	H	H
233		H	H	Me	H	H	H
234		H	H	H	CN	H	H
235		H	H	Cl	H	H	H
236		H	H	H	OMe	H	H

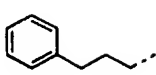
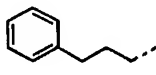
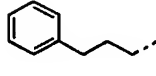
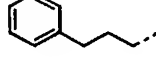
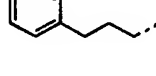
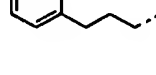
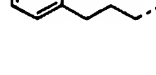
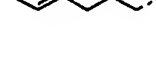
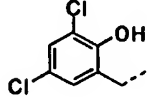
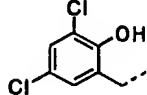
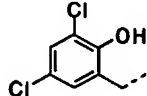
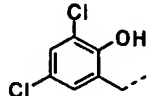
264

237		H	H	H	COOMe	H	H
238		H	H	H	H	Cl	H
239		H	H	H	H	COOMe	H
240		H	H	H	H	H	Cl
241		H	H	H	OCF3	H	H
242		H	H	COOMe	H	H	H
243		H	H	H	CF3	H	H
244		H	H	H	Me	H	H
245		H	H	H	F	H	H
246		H	H	H	OH	H	H
247		H	H	H	NO2	H	H
248		H	H	H	F	F	H

265

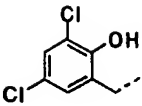
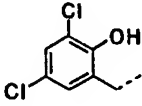
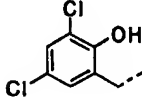
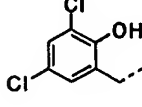
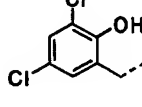
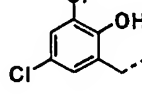
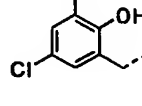
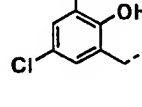
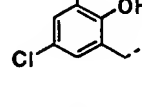
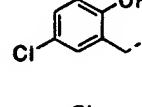
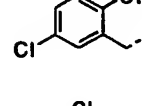
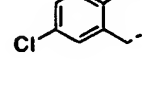
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250		H	H	Me	H	H	H
251		H	H	H	CN	H	H
252		H	H	Cl	H	H	H
253		H	H	H	OMe	H	H
254		H	H	H	COOMe	H	H
255		H	H	H	H	Cl	H
256		H	H	H	H	COOMe	H
257		H	H	H	H	H	Cl
258		H	H	H	OCF3	H	H
259		H	H	COOMe	H	H	H
260		H	H	H	CF3	H	H

266

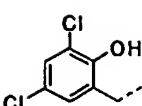
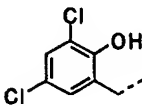
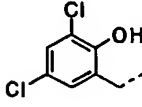
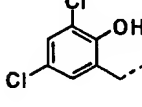
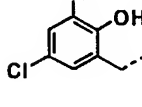
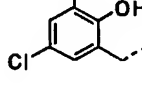
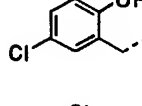
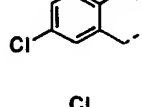
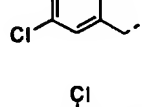
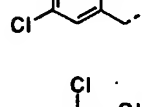
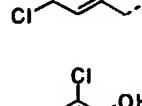
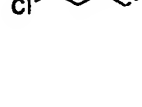
261		H	H	H	Me	H	H
262		H	H	H	F	H	H
263		H	H	H	OH	H	H
264		H	H	H	NO2	H	H
265		H	H	H	F	F	H
266		H	H	F	H	H	H
267		H	H	Me	H	H	H
268		H	H	H	CN	H	H
269		H	H	H	H	H	COOMe
270		H	H	H	H	F	H
271		H	H	H	H	H	F
272		H	H	H	H	Me	H



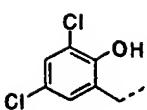
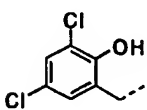
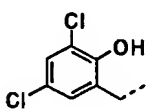
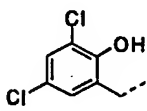
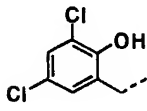
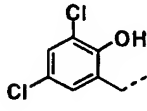
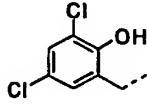
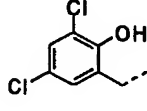
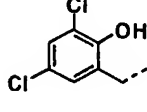
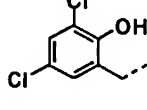
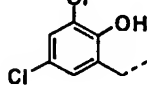
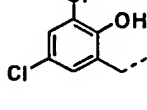
267

273		H	H	H	H	H	Me
274		H	H	OMe	H	H	H
275		H	H	H	H	OMe	H
276		H	H	H	H	H	OMe
277		H	H	CF3	H	H	H
278		H	H	H	H	CF3	H
279		H	H	H	H	H	CF3
280		H	H	OH	H	H	H
281		H	H	H	H	OH	H
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283		H	H	OCF3	H	H	H
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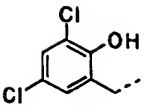
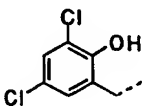
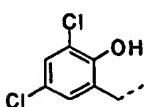
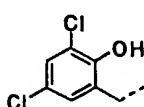
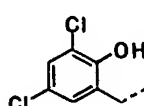
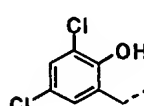
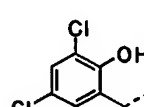
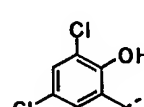
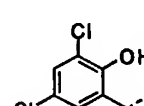
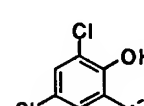
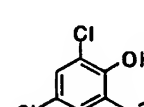
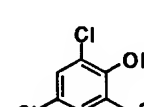
268

285		H	H	H	H	H	OCF3
286		H	H	NO2	H	H	H
287		H	H	H	H	NO2	H
288		H	H	H	H	H	NO2
289		H	H	CN	H	H	H
290		H	H	H	H	CN	H
291		H	H	H	H	H	CN
292		H	H	Br	H	H	H
293		H	H	H	Br	H	H
294		H	H	H	H	Br	H
295		H	H	H	H	H	Br
296		H	H	COOH	H	H	H

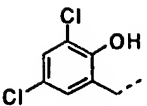
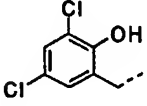
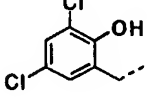
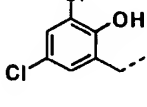
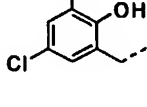
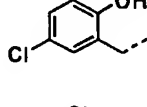
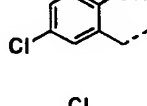
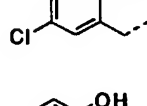
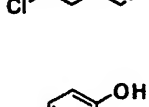
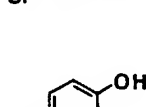
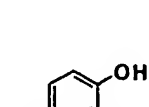

269

297		H	H	H	COOH	H	H
298		H	H	H	H	COOH	H
299		H	H	H	H	H	COOH
300		H	H	NHCOMe	H	H	H
301		H	H	H	NHCOMe	H	H
302		H	H	H	H	NHCOMe	H
303		H	H	H	H	H	NHCOMe
304		H	H	SO2NH2	H	H	H
305		H	H	H	SO2NH2	H	H
306		H	H	H	H	SO2NH2	H
307		H	H	H	H	H	SO2NH2
308		H	H	Me	Me	H	H

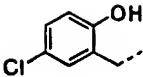
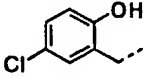
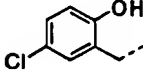
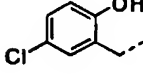
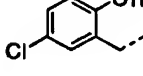
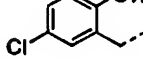
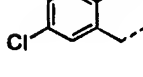
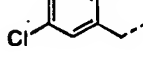
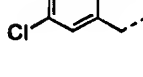
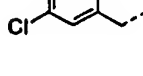
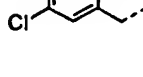
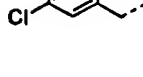
270

309		H	H	Me	H	Me	H
310		H	H	H	Me	Me	H
311		H	H	F	F	H	H
312		H	H	F	H	F	H
313		H	H	H	F	F	H
314		H	H	Cl	Cl	H	H
315		H	H	Cl	H	Cl	H
316		H	H	H	Cl	Cl	H
317		H	H	Me	F	H	H
318		H	H	Me	Cl	H	H
319		H	H	Me	OH	H	H
320		H	H	Me	OMe	H	H

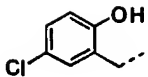
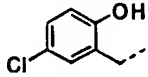
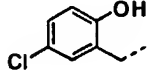
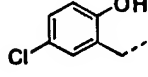
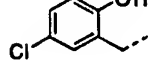
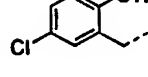
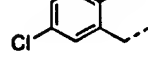
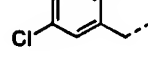
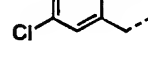
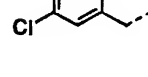
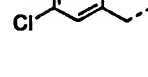
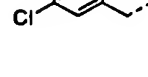
271

321		H	H	F	Me	H	H
322		H	H	F	Cl	H	H
323		H	H	F	OH	H	H
324		H	H	F	OMe	H	H
325		H	H	Cl	Me	H	H
326		H	H	Cl	F	H	H
327		H	H	Cl	OH	H	H
328		H	H	Cl	OMe	H	H
329		H	H	H	H	H	COOMe
330		H	H	H	H	F	H
331		H	H	H	H	H	F
332		H	H	H	H	Me	H

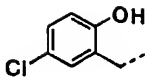
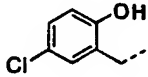
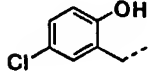
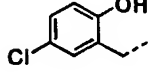
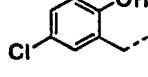
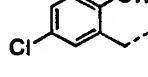
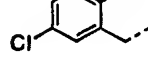
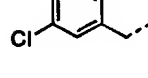
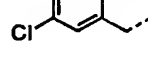
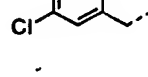
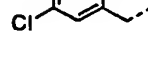
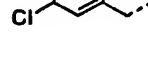
272

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335		H	H	H	H	OMe	H
336		H	H	H	H	H	OMe
337		H	H	CF3	H	H	H
338		H	H	H	H	CF3	H
339		H	H	H	H	H	CF3
340		H	H	OH	H	H	H
341		H	H	H	H	OH	H
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273

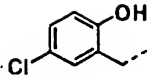
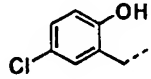
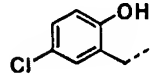
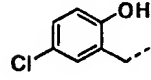
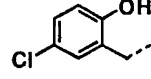
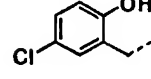
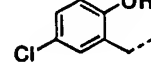
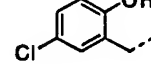
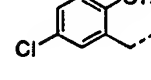
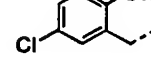
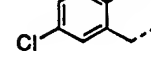
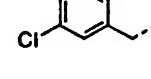
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346		H	H	NO2	H	H	H
347		H	H	H	H	NO2	H
348		H	H	H	H	H	NO2
349		H	H	CN	H	H	H
350		H	H	H	H	CN	H
351		H	H	H	H	H	CN
352		H	H	Br	H	H	H
353		H	H	H	Br	H	H
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355		H	H	H	H	H	Br
356		H	H	COOH	H	H	H

274

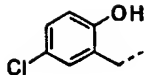
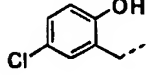
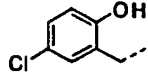
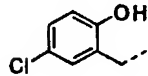
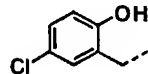
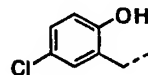
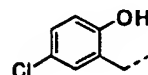
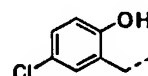
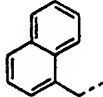
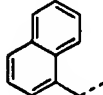
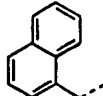
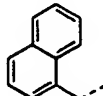
357		H	H	H	COOH	H	H
358		H	H	H	H	COOH	H
359		H	H	H	H	H	COOH
360		H	H	NHCOMe	H	H	H
361		H	H	H	NHCOMe	H	H
362		H	H	H	H	NHCOMe	H
363		H	H	H	H	H	NHCOMe
364		H	H	SO2NH2	H	H	H
365		H	H	H	SO2NH2	H	H
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367		H	H	H	H	H	SO2NH2
368		H	H	Me	Me	H	H



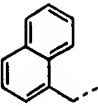
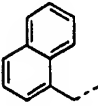
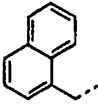
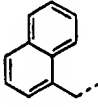
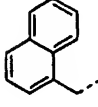
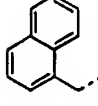
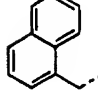
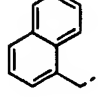
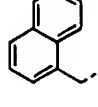
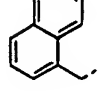
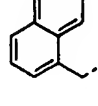
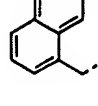
275

369		H	H	Me	H	Me	H
370		H	H	H	Me	Me	H
371		H	H	F	F	H	H
372		H	H	F	H	F	H
373		H	H	H	F	F	H
374		H	H	Cl	Cl	H	H
375		H	H	Cl	H	Cl	H
376		H	H	H	Cl	Cl	H
377		H	H	Me	F	H	H
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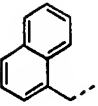
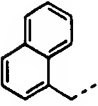
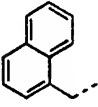
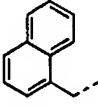
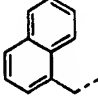
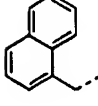
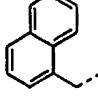
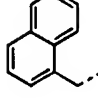
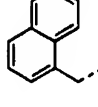
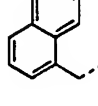
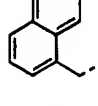
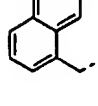
276

381		H	H	F	Me	H	H
382		H	H	F	Cl	H	H
383		H	H	F	OH	H	H
384		H	H	F	OMe	H	H
385		H	H	Cl	Me	H	H
386		H	H	Cl	F	H	H
387		H	H	Cl	OH	H	H
388		H	H	Cl	OMe	H	H
389		H	H	H	H	H	COOMe
390		H	H	H	H	F	H
391		H	H	H	H	H	F
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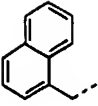
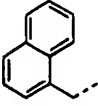
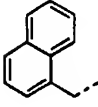
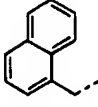
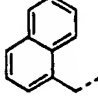
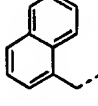
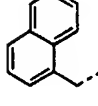
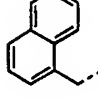
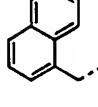
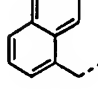
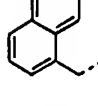
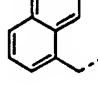
277

393		H	H	H	H	H	Me
394		H	H	OMe	H	H	H
395		H	H	H	H	OMe	H
396		H	H	H	H	H	OMe
397		H	H	CF3	H	H	H
398		H	H	H	H	CF3	H
399		H	H	H	H	H	CF3
400		H	H	OH	H	H	H
401		H	H	H	H	OH	H
402		H	H	H	H	H	OH
403		H	H	OCF3	H	H	H
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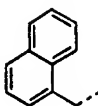
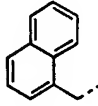
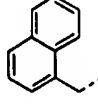
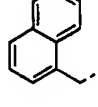
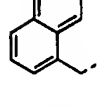
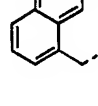
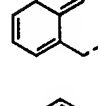
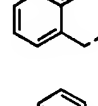
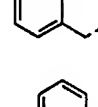
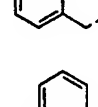
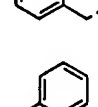
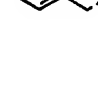
278

405		H	H	H	H	H	OCF3
406		H	H	NO2	H	H	H
407		H	H	H	H	NO2	H
408		H	H	H	H	H	NO2
409		H	H	CN	H	H	H
410		H	H	H	H	CN	H
411		H	H	H	H	H	CN
412		H	H	Br	H	H	H
413		H	H	H	Br	H	H
414		H	H	H	H	Br	H
415		H	H	H	H	H	Br
416		H	H	COOH	H	H	H

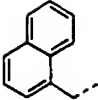
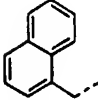
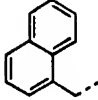
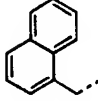
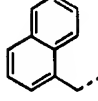

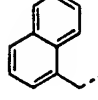
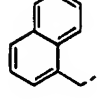
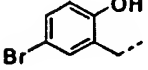
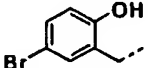
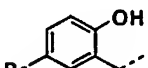
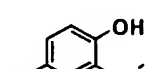
279

417		H	H	H	COOH	H	H
418		H	H	H	H	COOH	H
419		H	H	H	H	H	COOH
420		H	H	NHCOMe	H	H	H
421		H	H	H	NHCOMe	H	H
422		H	H	H	H	NHCOMe	H
423		H	H	H	H	H	NHCOMe
424		H	H	SO <sub>2</sub> NH <sub>2</sub>	H	H	H
425		H	H	H	SO <sub>2</sub> NH <sub>2</sub>	H	H
426		H	H	H	H	SO <sub>2</sub> NH <sub>2</sub>	H
427		H	H	H	H	H	SO <sub>2</sub> NH <sub>2</sub>
428		H	H	Me	Me	H	H

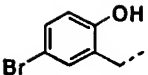
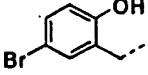
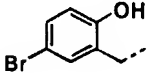
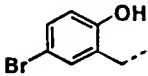
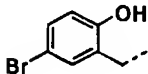
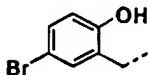
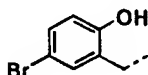
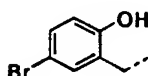
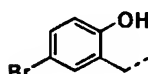
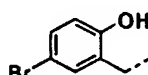
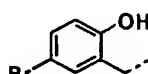
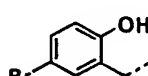
280

429		H	H	Me	H	Me	H
430		H	H	H	Me	Me	H
431		H	H	F	F	H	H
432		H	H	F	H	F	H
433		H	H	H	F	F	H
434		H	H	Cl	Cl	H	H
435		H	H	Cl	H	Cl	H
436		H	H	H	Cl	Cl	H
437		H	H	Me	F	H	H
438		H	H	Me	Cl	H	H
439		H	H	Me	OH	H	H
440		H	H	Me	OMe	H	H

281

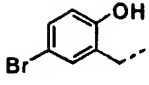
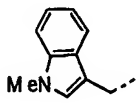
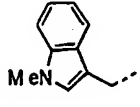
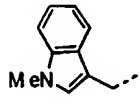
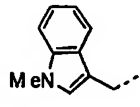
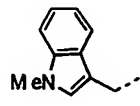
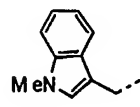
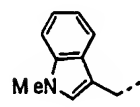
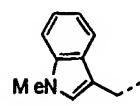
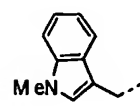
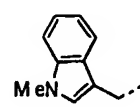
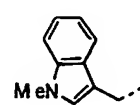
441		H	H	F	Me	H	H
442		H	H	F	Cl	H	H
443		H	H	F	OH	H	H
444		H	H	F	OMe	H	H
445		H	H	Cl	Me	H	H
446		H	H	Cl	F	H	H
447		H	H	Cl	OH	H	H
448		H	H	Cl	OMe	H	H
449		H	H	Cl	H	H	H
450		H	H	H	OMe	H	H
451		H	H	H	COOMe	H	H
452		H	H	H	H	Cl	H

282

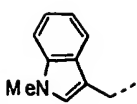
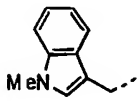
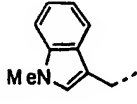
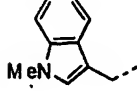
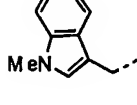
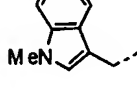
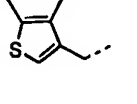
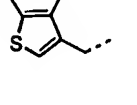
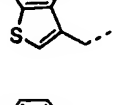
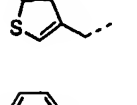
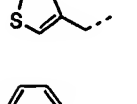
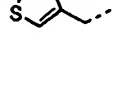
453		H	H	H	H	COOMe	H
454		H	H	H	H	H	Cl
455		H	H	H	OCF3	H	H
456		H	H	COOMe	H	H	H
457		H	H	H	CF3	H	H
458		H	H	H	Me	H	H
459		H	H	H	F	H	H
460		H	H	H	OH	H	H
461		H	H	H	NO2	H	H
462		H	H	H	F	F	H
463		H	H	F	H	H	H
464		H	H	Me	H	H	H



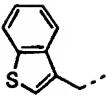
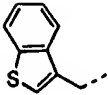
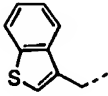
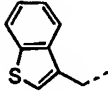
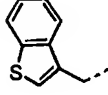
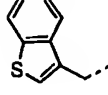
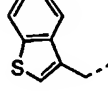
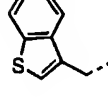
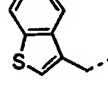
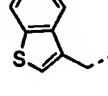
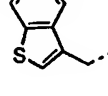
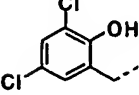
283

465		H	H	H	CN	H	H
466		H	H	Cl	H	H	H
467		H	H	H	OMe	H	H
468		H	H	H	COOMe	H	H
469		H	H	H	H	Cl	H
470		H	H	H	H	COOMe	H
471		H	H	H	H	H	Cl
472		H	H	H	OCF3	H	H
473		H	H	COOMe	H	H	H
474		H	H	H	CF3	H	H
475		H	H	H	Me	H	H
476		H	H	H	F	H	H

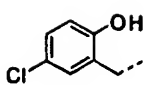
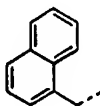
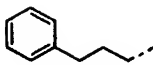
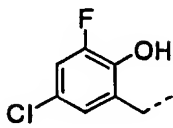
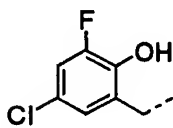
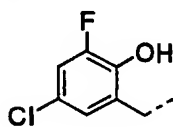
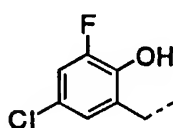
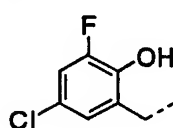
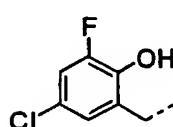
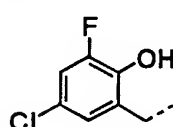
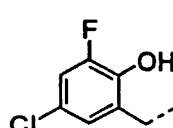
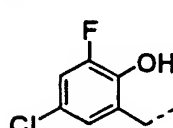
284

477		H	H	H	OH	H	H
478		H	H	H	NO <sub>2</sub>	H	H
479		H	H	H	F	F	H
480		H	H	F	H	H	H
481		H	H	Me	H	H	H
482		H	H	H	CN	H	H
483		H	H	Cl	H	H	H
484		H	H	H	OMe	H	H
485		H	H	H	COOMe	H	H
486		H	H	H	H	Cl	H
487		H	H	H	H	COOMe	H
488		H	H	H	H	H	Cl

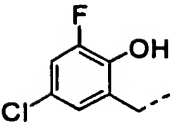
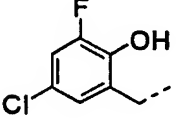
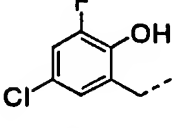
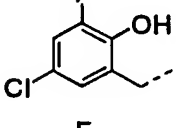
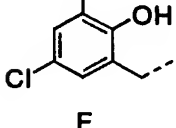
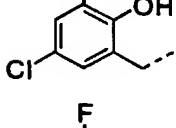
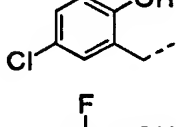
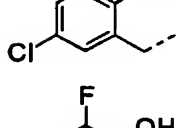
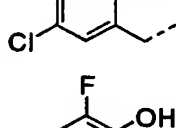
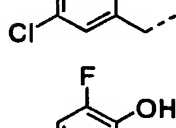
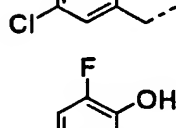
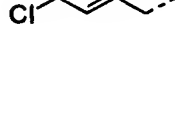
285

489		H	H	H	OCF3	H	H
490		H	H	COOMe	H	H	H
491		H	H	H	CF3	H	H
492		H	H	H	Me	H	H
493		H	H	H	F	H	H
494		H	H	H	OH	H	H
495		H	H	H	NO2	H	H
496		H	H	H	F	F	H
497		H	H	F	H	H	H
498		H	H	Me	H	H	H
499		H	H	H	CN	H	H
500		H	Me	H	H	H	H

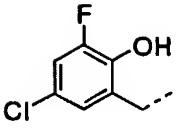
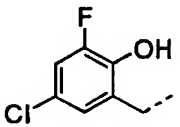
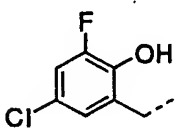
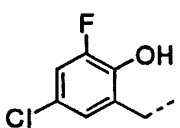
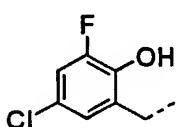
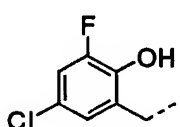
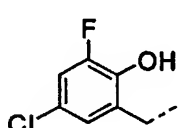
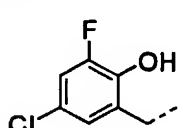
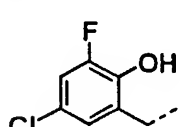
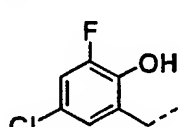
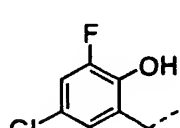
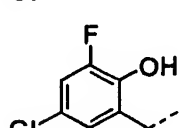
286

501		H	Me	H	H	H	H
502		H	Me	H	H	H	H
503		H	Me	H	H	H	H
504		H	H	H	H	H	H
505		H	H	F	H	H	H
506		H	H	Cl	H	H	H
507		H	H	Me	H	H	H
508		H	H	Et	H	H	H
509		H	H	OMe	H	H	H
510		H	H	OEt	H	H	H
511		H	H	CF3	H	H	H
512		H	H	OCF3	H	H	H

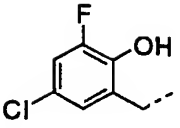
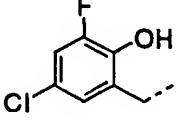
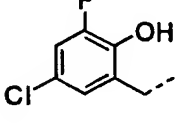
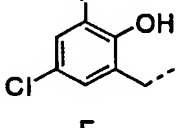
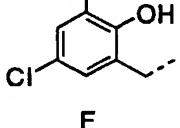
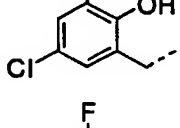
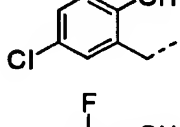
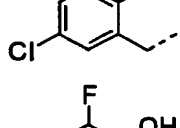
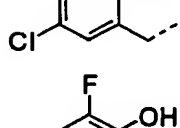
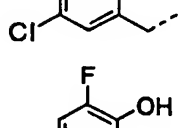
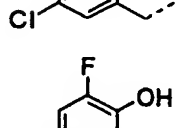
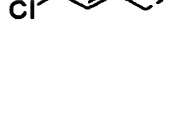
287

513		H	H	NO2	H	H	H
514		H	H	NH2	H	H	H
515		H	H	OH	H	H	H
516		H	H	CN	H	H	H
517		H	H	COMe	H	H	H
518		H	H	COOMe	H	H	H
519		H	H	H	F	H	H
520		H	H	H	Cl	H	H
521		H	H	H	Me	H	H
522		H	H	H	Et	H	H
523		H	H	H	OMe	H	H
524		H	H	H	OEt	H	H

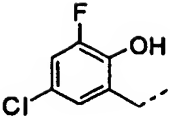
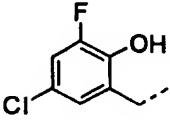
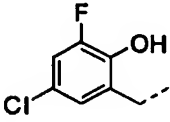
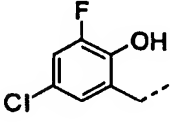
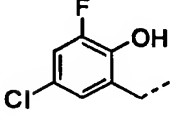
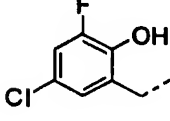
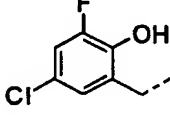
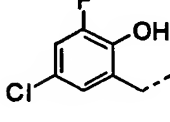
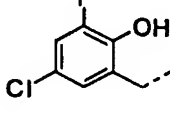
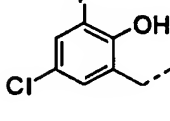
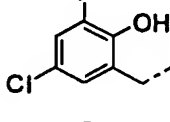
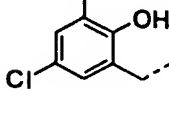
288

525		H	H	H	CF3	H	H
526		H	H	H	OCF3	H	H
527		H	H	H	NO2	H	H
528		H	H	H	NH2	H	H
529		H	H	H	OH	H	H
530		H	H	H	CN	H	H
531		H	H	H	COMe	H	H
532		H	H	H	COOMe	H	H
533		H	H	F	F	H	H
534		H	H	F	Cl	H	H
535		H	H	F	Me	H	H
536		H	H	F	Et	H	H

289

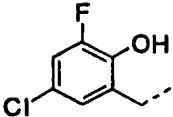
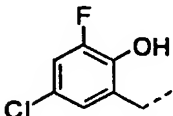
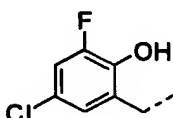
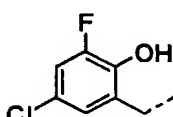
537		H	H	F	OMe	H	H
538		H	H	F	OEt	H	H
539		H	H	F	CF3	H	H
540		H	H	F	OCF3	H	H
541		H	H	Cl	F	H	H
542		H	H	Cl	Cl	H	H
543		H	H	Cl	Me	H	H
544		H	H	Cl	Et	H	H
545		H	H	Cl	OMe	H	H
546		H	H	Cl	OEt	H	H
547		H	H	Cl	CF3	H	H
548		H	H	Cl	OCF3	H	H

290

549		H	H	Me	F	H	H
550		H	H	Me	Cl	H	H
551		H	H	Me	Me	H	H
552		H	H	Me	Et	H	H
553		H	H	Me	OMe	H	H
554		H	H	Me	OEt	H	H
555		H	H	Me	CF3	H	H
556		H	H	Me	OCF3	H	H
557		H	H	OMe	F	H	H
558		H	H	OMe	Cl	H	H
559		H	H	OMe	Me	H	H
560		H	H	OMe	Et	H	H

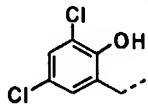
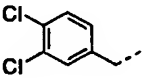
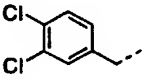
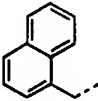
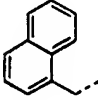
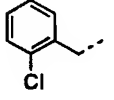
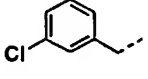
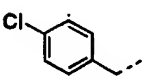
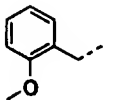
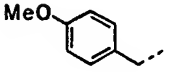
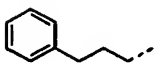


291

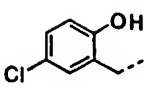
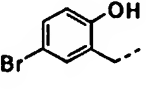
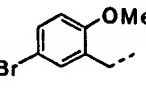
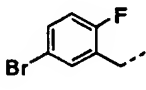
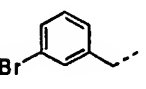
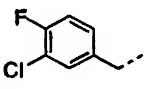
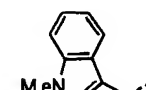
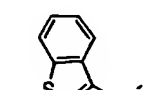
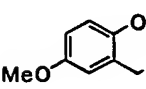
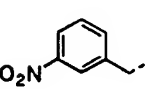
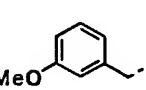
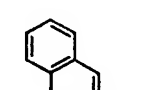
561		H	H	OMe	OMe	H	H
562		H	H	OMe	OEt	H	H
563		H	H	OMe	CF3	H	H
564		H	H	OMe	OCF3	H	H

X = -CO-, q = 0, r = 0, Y = -S-

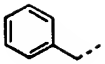
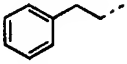
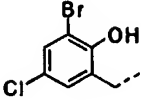
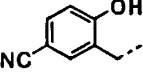
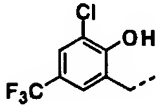
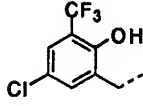

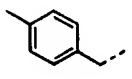
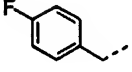
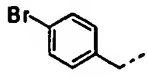
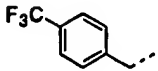
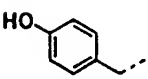
表 5

compnd NO.5—	R1-(CH <sub>2</sub> ) <sub>p</sub> —	R2	R3	R6	R7
1		H	H	H	H
2		H	H	H	H
3		H	H	H	H
4		H	H	H	H
5		H	H	H	H
6		H	H	H	H
7		H	H	H	H
8		H	H	H	H
9		H	H	H	H
10		H	H	H	H
11		H	H	H	H

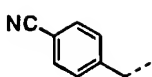
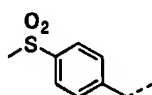
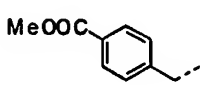
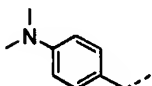
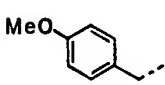
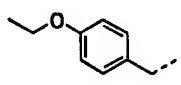
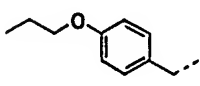
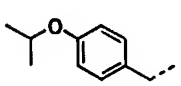
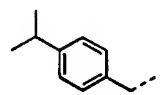
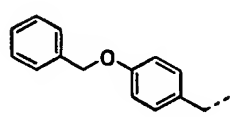
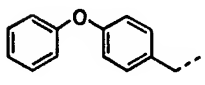
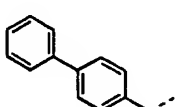
293

12		H	H	H	H
13		H	H	H	H
14		H	H	H	H
15		H	H	H	H
16		H	H	H	H
17		H	H	H	H
18		H	H	H	H
19		H	H	H	H
20		H	H	H	H
21		H	H	H	H
22		H	H	H	H
23		H	H	H	H

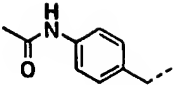
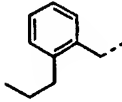
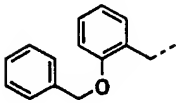
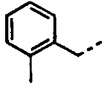
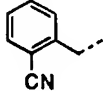
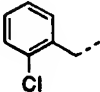
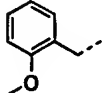
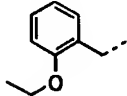
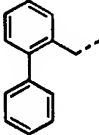
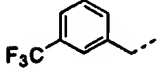
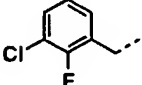
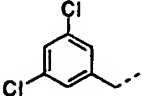
294

24		H	H	H	H
25		H	H	H	H
26		H	H	H	H
27		H	H	H	H
28		H	H	H	H
29		H	H	H	H
30		H	H	H	H
31		H	H	H	H
32		H	H	H	H
33		H	H	H	H
34		H	H	H	H
35		H	H	H	H

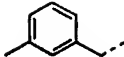
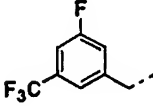
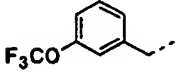
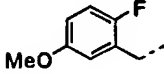
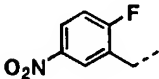
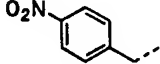
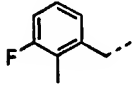
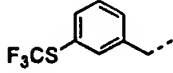
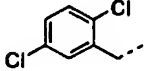
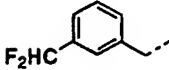
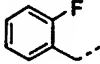
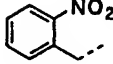
295

36		H	H	H	H
37		H	H	H	H
38		H	H	H	H
39		H	H	H	H
40		H	H	H	H
41		H	H	H	H
42		H	H	H	H
43		H	H	H	H
44		H	H	H	H
45		H	H	H	H
46		H	H	H	H
47		H	H	H	H

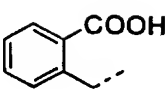
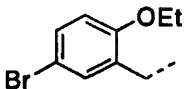
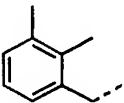
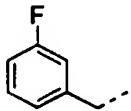
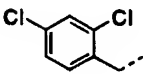
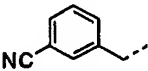
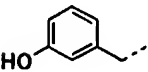
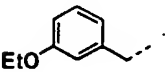
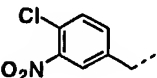
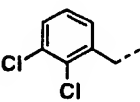
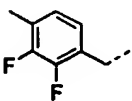
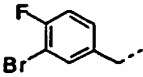
296

48		H	H	H	H
49		H	H	H	H
50		H	H	H	H
51		H	H	H	H
52		H	H	H	H
53		H	H	H	H
54		H	H	H	H
55		H	H	H	H
56		H	H	H	H
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58		H	H	H	H
59		H	H	H	H

297

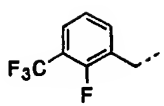
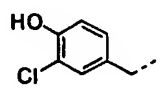
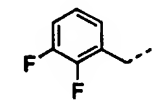
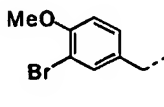
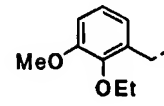
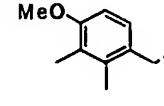
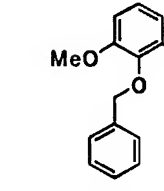
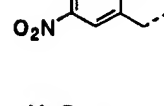
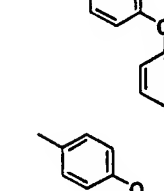
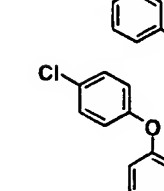

60		H	H	H	H
61		H	H	H	H
62		H	H	H	H
63		H	H	H	H
64		H	H	H	H
65		H	H	H	H
66		H	H	H	H
67		H	H	H	H
68		H	H	H	H
69		H	H	H	H
70		H	H	H	H
71		H	H	H	H

298

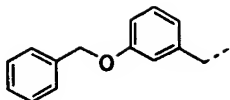
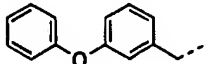
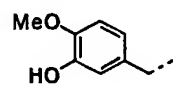
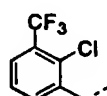
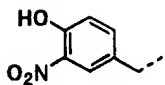
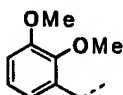
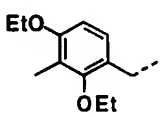
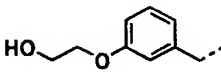
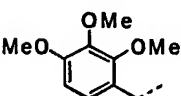
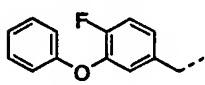
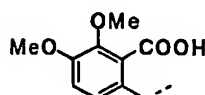
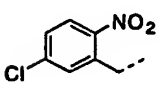
72		H	H	H	H
73		H	H	H	H
74		H	H	H	H
75		H	H	H	H
76		H	H	H	H
77		H	H	H	H
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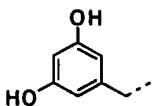
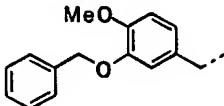
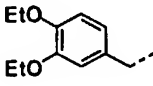
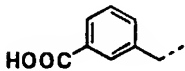
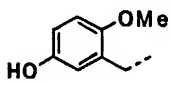
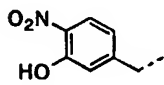
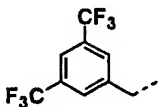
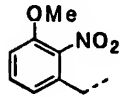
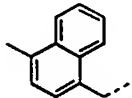
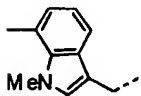
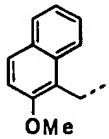
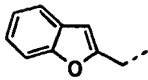
299

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89		H	H	H	H
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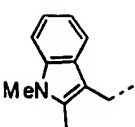
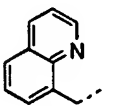
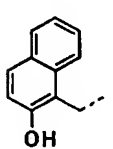
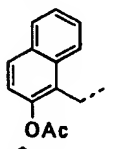
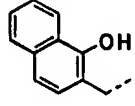
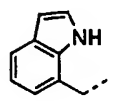
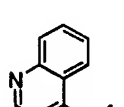
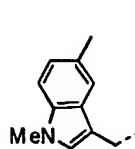
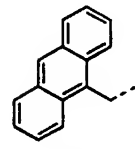
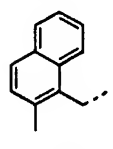
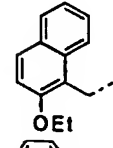
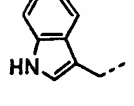
300

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100		H	H	H	H
101		H	H	H	H
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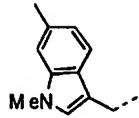
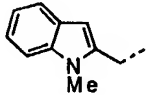
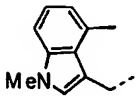
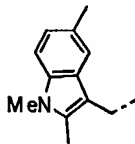
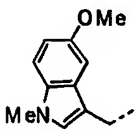
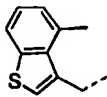
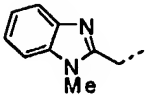
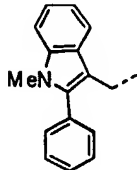
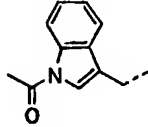
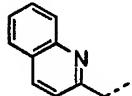
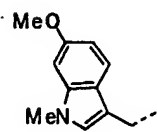
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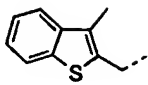
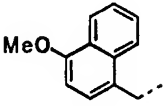
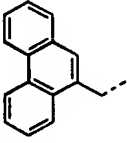
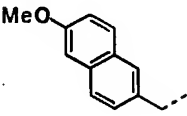
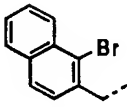
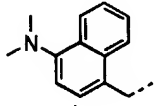
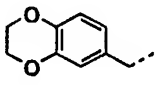
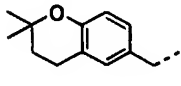
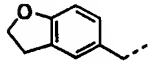
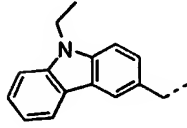
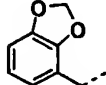
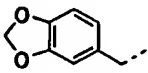
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302

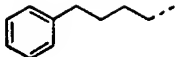
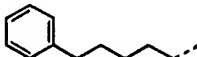
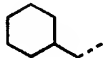
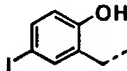
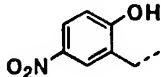
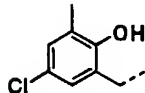
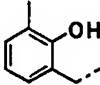
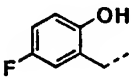
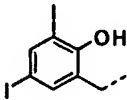
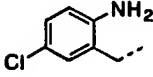
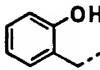
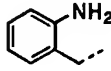
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303

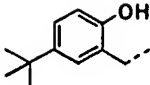
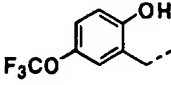
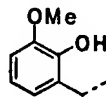
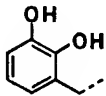
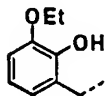
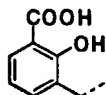
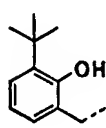
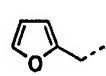
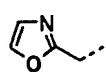
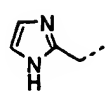
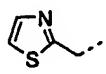
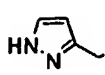
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305

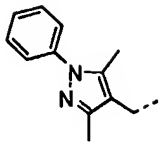
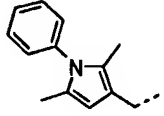
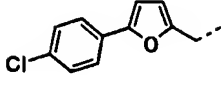





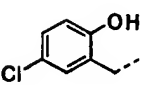
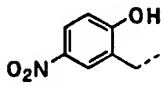
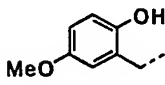
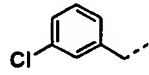
154		H	H	H	H
155		H	H	H	H
156		H	H	H	H
157		H	H	H	H
158		H	H	H	H
159		H	H	H	H
160		H	H	H	H
161		H	H	H	H
162		H	H	H	H
163		H	H	H	H
164		H	H	H	H
165		H	H	H	H

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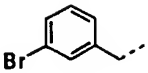
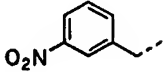
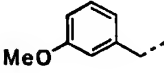
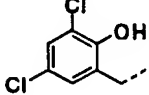
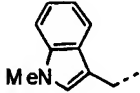
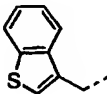
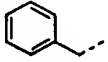
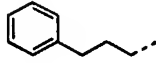
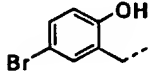
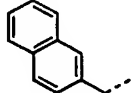
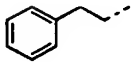
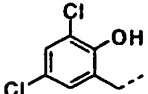
166		H	H	H	H
167		H	H	H	H
168		H	H	H	H
169		H	H	H	H
170		H	H	H	H
171		H	H	H	H
172		H	H	H	H
173		H	H	H	H
174		H	H	H	H
175		H	H	H	H
176		H	H	H	H
177		H	H	H	H



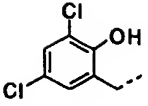
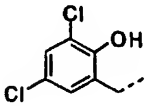
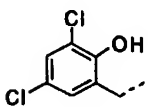
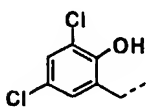
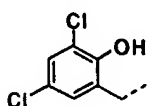
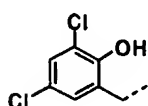
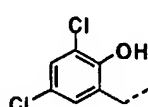
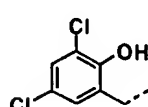
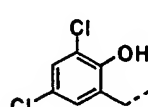
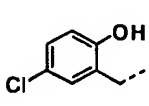
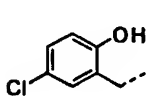
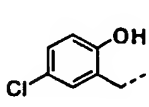
307

178		H	H	H	H
179		H	H	H	H
180		H	H	H	H
181		H	H	H	H
182		H	H	H	H
183		H	H	H	H
184		H	H	H	H
185		H	H	H	H
186		H	H	H	H
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188		H	H	H	H
189		H	H	H	H

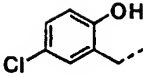
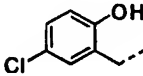
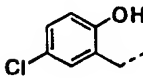
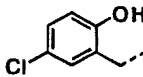
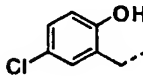
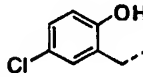
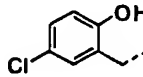
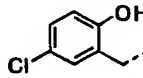
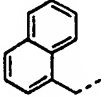
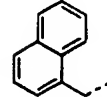
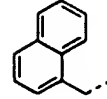
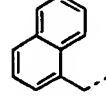
308

190		H	H	H	H
191		H	H	H	H
192		H	H	H	H
193		H	H	H	H
194		H	H	H	H
195		H	H	H	H
196		H	H	H	H
197		H	H	H	H
198		H	H	H	H
199		H	H	H	H
200		H	H	H	H
201		H	H	Cl	H

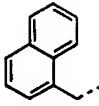
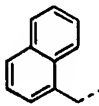
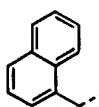
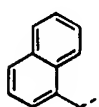
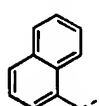
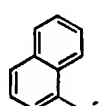
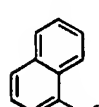
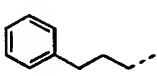
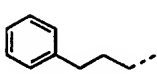
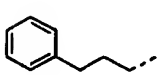
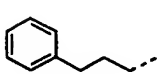
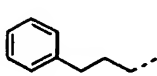
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202		H	H	COOMe	H
203		H	H	OMe	H
204		H	H	OCF3	H
205		H	H	CF3	H
206		H	H	Me	H
207		H	H	F	H
208		H	H	NO2	H
209		H	H	CN	H
210		H	H	OH	H
211		H	H	H	H
212		H	H	Cl	H
213		H	H	COOMe	H

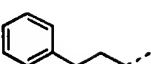
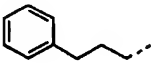
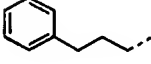
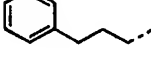
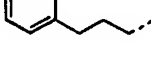
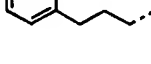
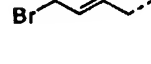





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214		H	H	OMe	H
215		H	H	OCF3	H
216		H	H	CF3	H
217		H	H	Me	H
218		H	H	F	H
219		H	H	NO2	H
220		H	H	CN	H
221		H	H	OH	H
222		H	H	H	H
223		H	H	Cl	H
224		H	H	COOMe	H
225		H	H	OMe	H

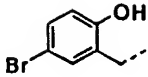
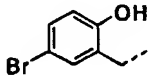
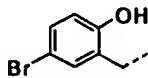
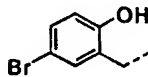
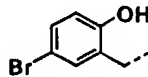
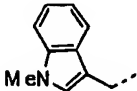
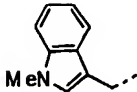
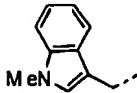
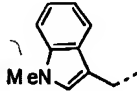
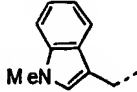
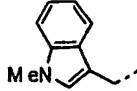
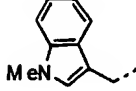
311

226		H	H	OCF3	H
227		H	H	CF3	H
228		H	H	Me	H
229		H	H	F	H
230		H	H	NO2	H
231		H	H	CN	H
232		H	H	OH	H
233		H	H	H	H
234		H	H	Cl	H
235		H	H	COOMe	H
236		H	H	OMe	H
237		H	H	OCF3	H

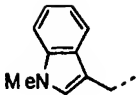
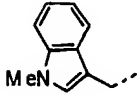
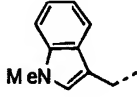
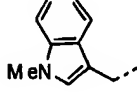
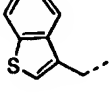
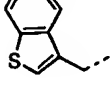
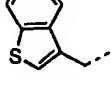
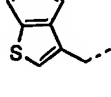
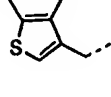
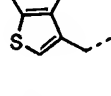
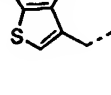
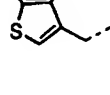
312

238		H	H	CF <sub>3</sub>	H
239		H	H	Me	H
240		H	H	F	H
241		H	H	NO <sub>2</sub>	H
242		H	H	CN	H
243		H	H	OH	H
244		H	H	H	H
245		H	H	Cl	H
246		H	H	COOMe	H
247		H	H	OMe	H
248		H	H	OCF <sub>3</sub>	H
249		H	H	CF <sub>3</sub>	H

313

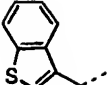
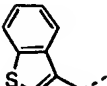
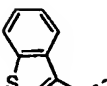
250		H	H	Me	H
251		H	H	F	H
252		H	H	NO2	H
253		H	H	CN	H
254		H	H	OH	H
255		H	H	H	H
256		H	H	Cl	H
257		H	H	COOMe	H
258		H	H	OMe	H
259		H	H	OCF3	H
260		H	H	CF3	H
261		H	H	Me	H

314

262		H	H	F	H
263		H	H	NO <sub>2</sub>	H
264		H	H	CN	H
265		H	H	OH	H
266		H	H	H	H
267		H	H	Cl	H
268		H	H	COOMe	H
269		H	H	OMe	H
270		H	H	OCF <sub>3</sub>	H
271		H	H	CF <sub>3</sub>	H
272		H	H	Me	H
273		H	H	F	H

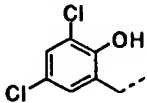
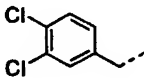
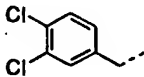
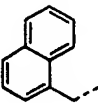
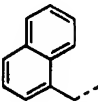
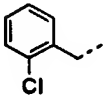
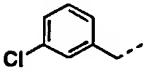
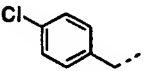
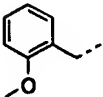
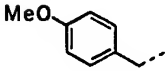


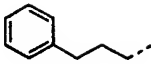
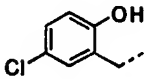
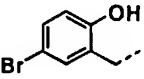
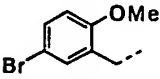
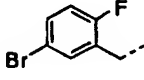
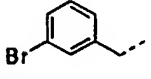
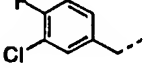
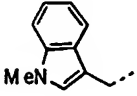
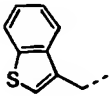
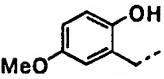
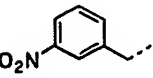
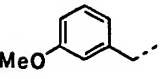
315

274		H	H	NO2	H
275		H	H	CN	H
276		H	H	OH	H

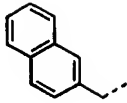
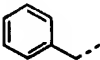
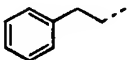
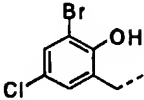
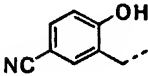
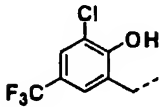
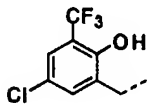
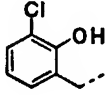
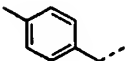
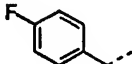
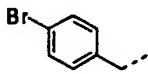
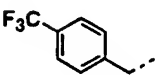
$X = -CO-, q = 0, r = 0, Y = -N(R8)-$ 

表 6

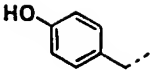
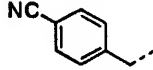
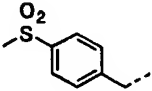
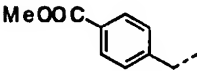
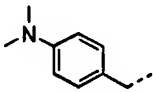
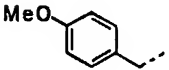
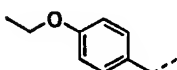
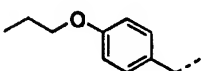
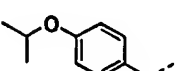
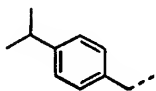
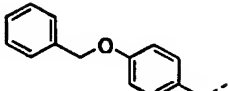
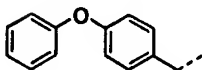
cmpnd NO.6—	R1-(CH <sub>2</sub> ) <sub>p</sub> —	R2	R3	R6	R7	R8
1		H	H	H	H	Me
2		H	H	H	H	Me
3		H	H	H	H	Me
4		H	H	H	H	Me
5		H	H	H	H	Me
6		H	H	H	H	Me
7		H	H	H	H	Me
8		H	H	H	H	Me
9		H	H	H	H	Me
10		H	H	H	H	Me

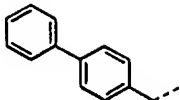
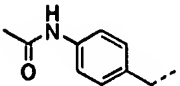
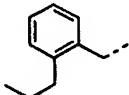
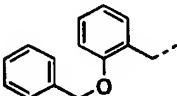
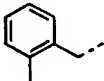
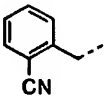
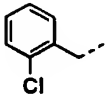
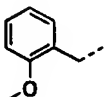
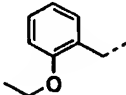
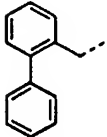
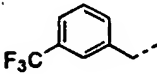
11		H	H	H	H	Me
12		H	H	H	H	Me
13		H	H	H	H	Me
14		H	H	H	H	Me
15		H	H	H	H	Me
16		H	H	H	H	Me
17		H	H	H	H	Me
18		H	H	H	H	Me
19		H	H	H	H	Me
20		H	H	H	H	Me
21		H	H	H	H	Me
22		H	H	H	H	Me

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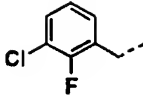
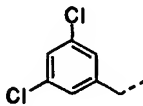
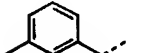
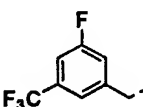
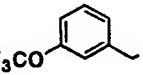
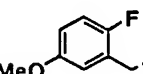
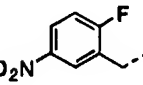
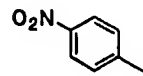
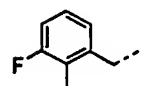
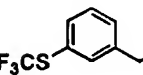
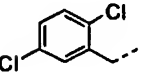
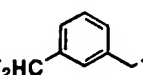
23		H	H	H	H	Me
24		H	H	H	H	Me
25		H	H	H	H	Me
26		H	H	H	H	Me
27		H	H	H	H	Me
28		H	H	H	H	Me
29		H	H	H	H	Me
30		H	H	H	H	Me
31		H	H	H	H	Me
32		H	H	H	H	Me
33		H	H	H	H	Me
34		H	H	H	H	Me

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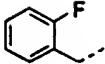
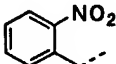
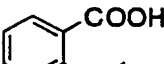
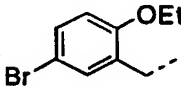
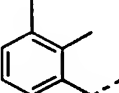
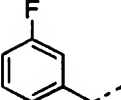
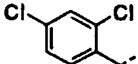
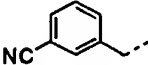
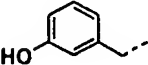
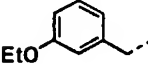
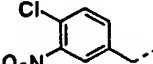
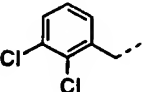
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40		H	H	H	H	Me
41		H	H	H	H	Me
42		H	H	H	H	Me
43		H	H	H	H	Me
44		H	H	H	H	Me
45		H	H	H	H	Me
46		H	H	H	H	Me

47		H	H	H	H	Me
48		H	H	H	H	Me
49		H	H	H	H	Me
50		H	H	H	H	Me
51		H	H	H	H	Me
52		H	H	H	H	Me
53		H	H	H	H	Me
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321

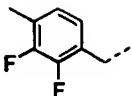
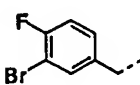
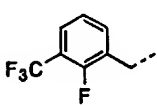
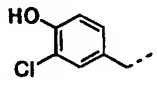
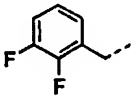
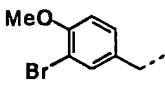
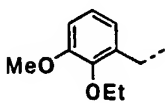
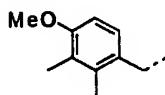
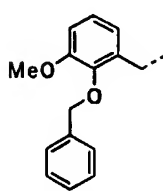
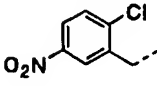
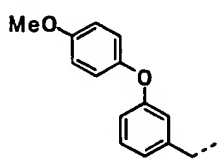
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63		H	H	H	H	Me
64		H	H	H	H	Me
65		H	H	H	H	Me
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67		H	H	H	H	Me
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322

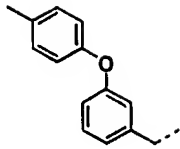
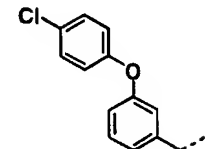
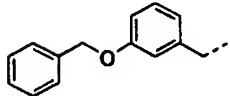
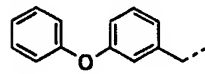
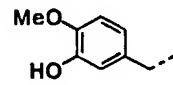
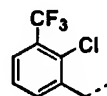
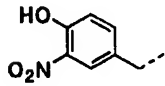
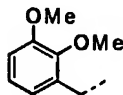
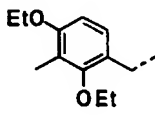
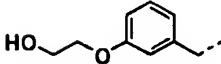
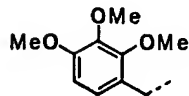
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74		H	H	H	H	Me
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76		H	H	H	H	Me
77		H	H	H	H	Me
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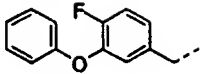
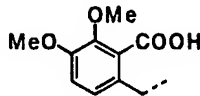
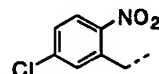
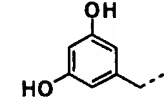
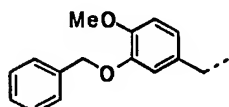
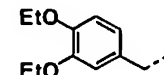
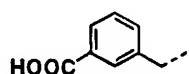
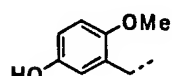
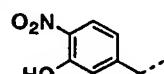
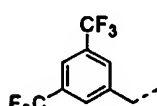
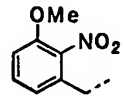
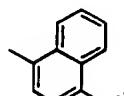
323

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84		H	H	H	H	Me
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87		H	H	H	H	Me
88		H	H	H	H	Me
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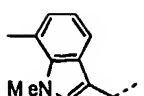
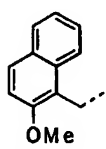
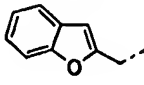
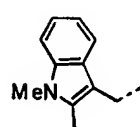
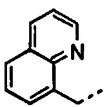
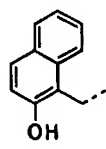
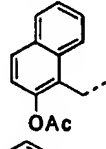
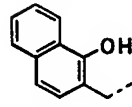
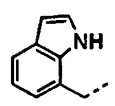
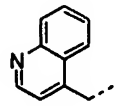
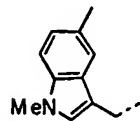
324

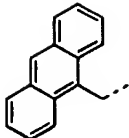
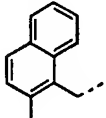
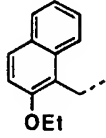
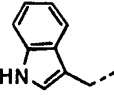
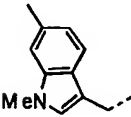
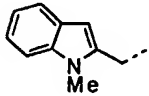
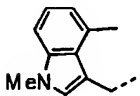
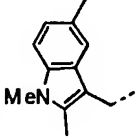
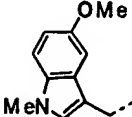
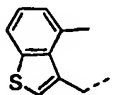
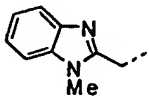
93		H	H	H	H	Me
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98		H	H	H	H	Me
99		H	H	H	H	Me
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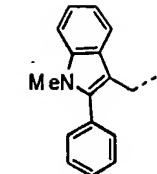
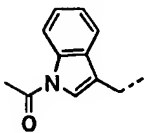
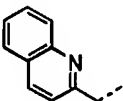
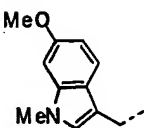
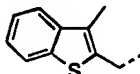
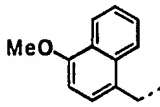
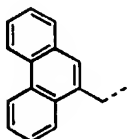
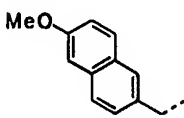
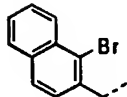
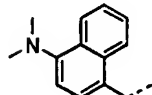
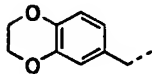
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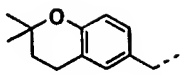
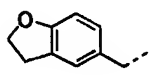
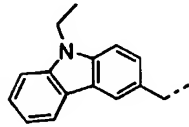
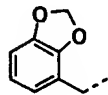
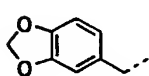
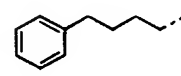
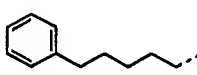
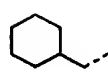
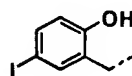
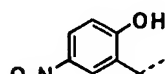
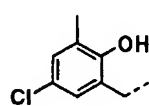
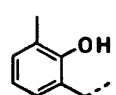
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111		H	H	H	H	Me
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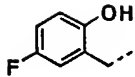
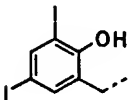
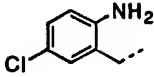
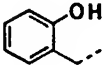
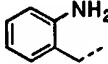
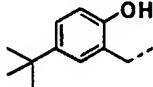
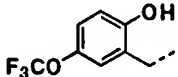
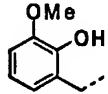
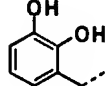
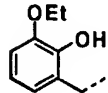
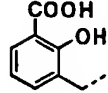
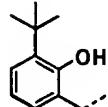
326

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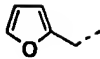
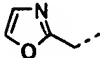
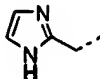
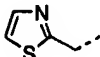
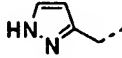
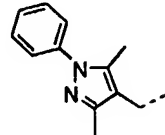
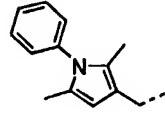
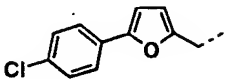
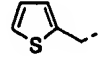
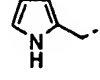
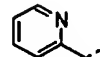
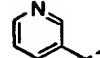
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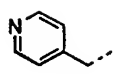
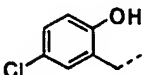
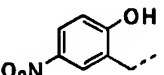
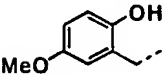
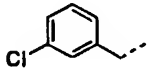
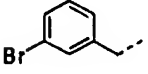
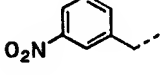
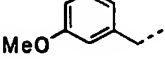
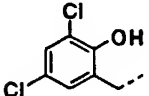
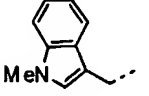
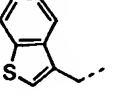

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144		H	H	H	H	Me
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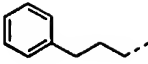
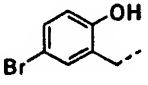
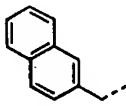
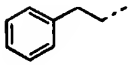
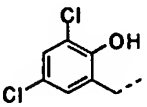
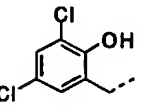
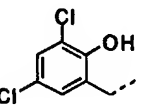
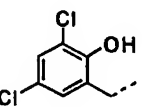
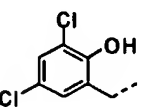
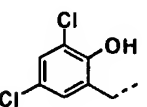
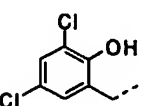
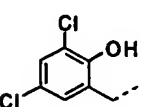
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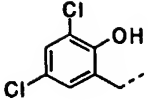
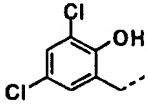
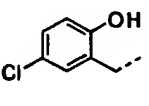
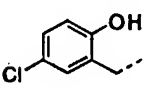
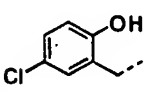
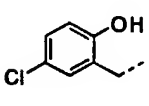
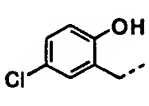
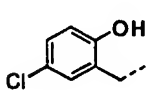
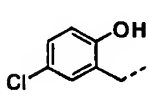
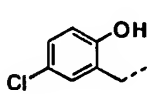
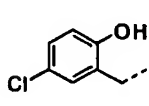
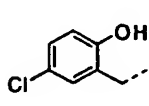
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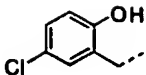











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180		H	H	H	H	Me
181		H	H	H	H	Me
182		H	H	H	H	Me
183		H	H	H	H	Me
184		H	H	H	H	Me

185		H	H	H	H	Me
186		H	H	H	H	Me
187		H	H	H	H	Me
188		H	H	H	H	Me
189		H	H	H	H	Me
190		H	H	H	H	Me
191		H	H	H	H	Me
192		H	H	H	H	Me
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194		H	H	H	H	Me
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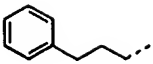
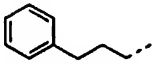
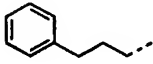
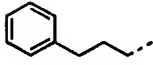
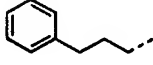
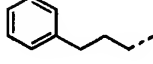
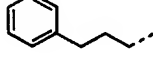
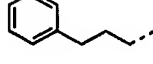
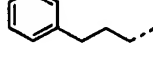
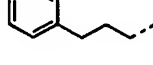
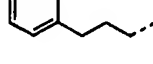
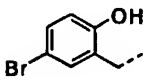
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198		H	H	H	H	Me
199		H	H	H	H	Me
200		H	H	H	H	Me
201		H	H	Cl	H	Me
202		H	H	COOMe	H	Me
203		H	H	OMe	H	Me
204		H	H	OCF3	H	Me
205		H	H	CF3	H	Me
206		H	H	Me	H	Me
207		H	H	F	H	Me
208		H	H	NO2	H	Me

209		H	H	CN	H	Me
210		H	H	OH	H	Me
211		H	H	H	H	Me
212		H	H	Cl	H	Me
213		H	H	COOMe	H	Me
214		H	H	OMe	H	Me
215		H	H	OCF3	H	Me
216		H	H	CF3	H	Me
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220		H	H	CN	H	Me

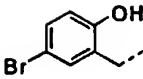
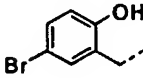
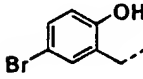
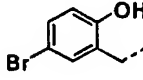
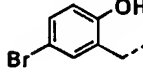
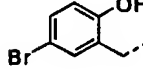
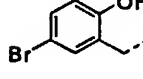
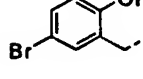
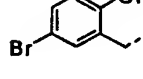
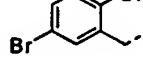
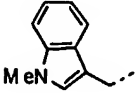
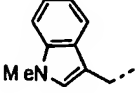
335

221		H	H	OH	H	Me
222		H	H	H	H	Me
223		H	H	Cl	H	Me
224		H	H	COOMe	H	Me
225		H	H	OMe	H	Me
226		H	H	OCF3	H	Me
227		H	H	CF3	H	Me
228		H	H	Me	H	Me
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230		H	H	NO2	H	Me
231		H	H	CN	H	Me
232		H	H	OH	H	Me

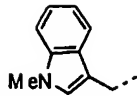
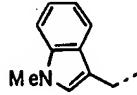
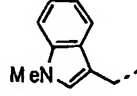
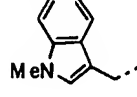
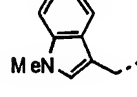
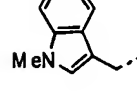
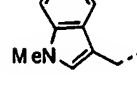
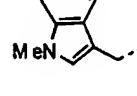
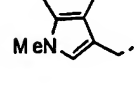
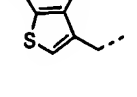
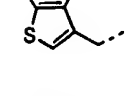
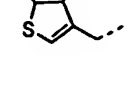
336

233		H	H	H	H	Me
234		H	H	Cl	H	Me
235		H	H	COOMe	H	Me
236		H	H	OMe	H	Me
237		H	H	OCF3	H	Me
238		H	H	CF3	H	Me
239		H	H	Me	H	Me
240		H	H	F	H	Me
241		H	H	NO2	H	Me
242		H	H	CN	H	Me
243		H	H	OH	H	Me
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337

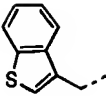
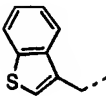
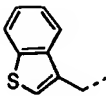
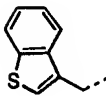
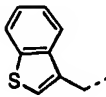
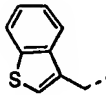
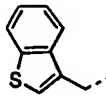
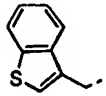
245		H	H	Cl	H	Me
246		H	H	COOMe	H	Me
247		H	H	OMe	H	Me
248		H	H	OCF3	H	Me
249		H	H	CF3	H	Me
250		H	H	Me	H	Me
251		H	H	F	H	Me
252		H	H	NO2	H	Me
253		H	H	CN	H	Me
254		H	H	OH	H	Me
255		H	H	H	H	Me
256		H	H	Cl	H	Me

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257		H	H	COOMe	H	Me
258		H	H	OMe	H	Me
259		H	H	OCF3	H	Me
260		H	H	CF3	H	Me
261		H	H	Me	H	Me
262		H	H	F	H	Me
263		H	H	NO2	H	Me
264		H	H	CN	H	Me
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268		H	H	COOMe	H	Me

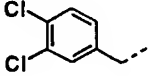
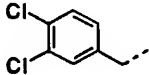
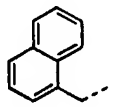
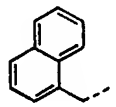
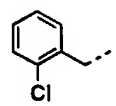
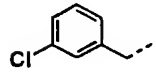
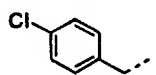
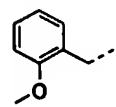
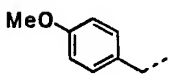
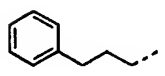


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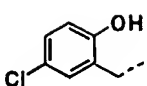
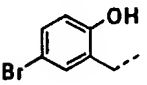
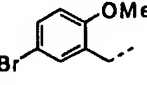
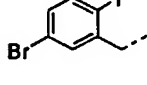
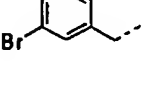
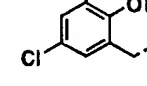
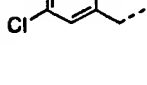
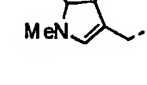
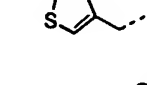
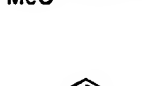
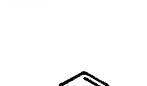

269		H	H	OMe	H	Me
270		H	H	OCF3	H	Me
271		H	H	CF3	H	Me
272		H	H	Me	H	Me
273		H	H	F	H	Me
274		H	H	NO2	H	Me
275		H	H	CN	H	Me
276		H	H	OH	H	Me

$$X = -CO-, q = 1, r = 0, Y = -(R4)C=C(R5)-$$

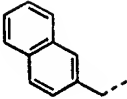

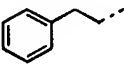
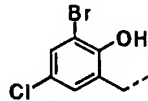
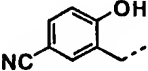
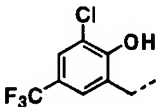
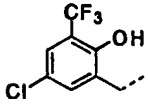
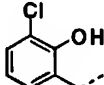
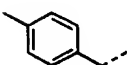
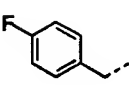
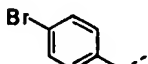
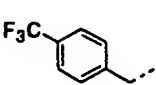
表 7

compnd NO.7-	R1-(CH <sub>2</sub> ) <sub>p</sub> --	R2	R3	R4	R5	R6	R7
1		H	H	H	H	H	H
2		H	H	H	Cl	H	H
3		H	H	H	H	H	H
4		H	H	H	Cl	H	H
5		H	H	H	H	H	H
6		H	H	H	H	H	H
7		H	H	H	H	H	H
8		H	H	H	H	H	H
9		H	H	H	H	H	H
10		H	H	H	H	H	H

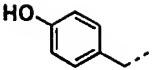
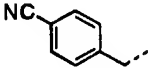
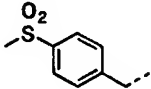
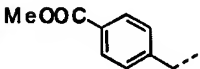
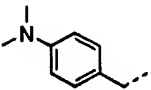
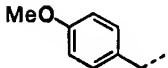
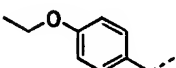
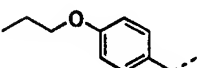
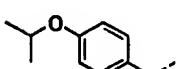
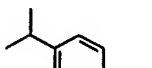
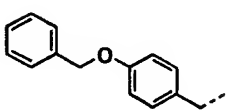
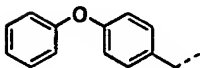
341

11		H	H	H	H	H	H
12		H	H	H	H	H	H
13		H	H	H	H	H	H
14		H	H	H	H	H	H
15		H	H	H	H	H	H
16		H	H	H	H	H	H
17		H	H	H	H	H	H
18		H	H	H	H	H	H
19		H	H	H	H	H	H
20		H	H	H	H	H	H
21		H	H	H	H	H	H
22		H	H	H	H	H	H

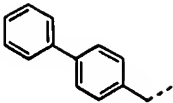
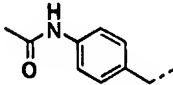
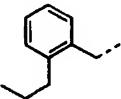
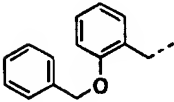

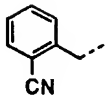
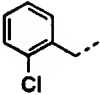

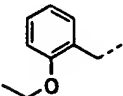
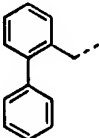
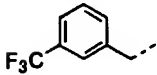
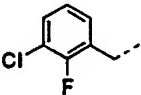
342

23		H	H	H	H	H	H
24		H	H	H	H	H	H
25		H	H	H	H	H	H
26		H	H	H	H	H	H
27		H	H	H	H	H	H
28		H	H	H	H	H	H
29		H	H	H	H	H	H
30		H	H	H	H	H	H
31		H	H	H	H	H	H
32		H	H	H	H	H	H
33		H	H	H	H	H	H
34		H	H	H	H	H	H

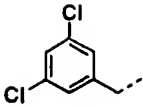
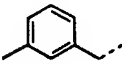
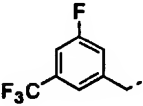
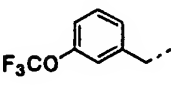
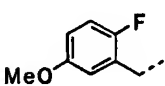
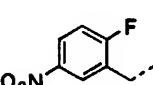
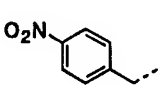
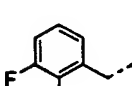
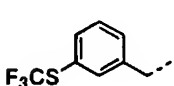
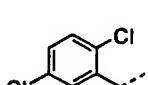
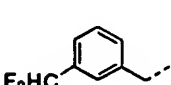
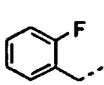
343

35		H	H	H	H	H	H
36		H	H	H	H	H	H
37		H	H	H	H	H	H
38		H	H	H	H	H	H
39		H	H	H	H	H	H
40		H	H	H	H	H	H
41		H	H	H	H	H	H
42		H	H	H	H	H	H
43		H	H	H	H	H	H
44		H	H	H	H	H	H
45		H	H	H	H	H	H
46		H	H	H	H	H	H

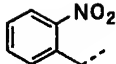
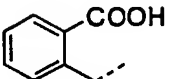
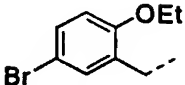
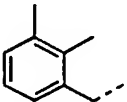
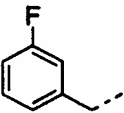
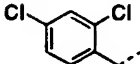
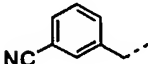
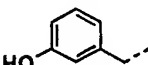
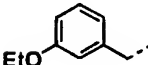
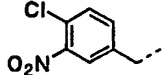
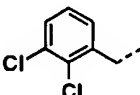
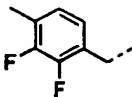
344

47		H	H	H	H	H	H
48		H	H	H	H	H	H
49		H	H	H	H	H	H
50		H	H	H	H	H	H
51		H	H	H	H	H	H
52		H	H	H	H	H	H
53		H	H	H	H	H	H
54		H	H	H	H	H	H
55		H	H	H	H	H	H
56		H	H	H	H	H	H
57		H	H	H	H	H	H
58		H	H	H	H	H	H

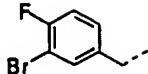
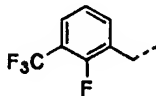
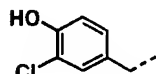
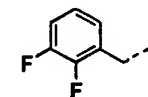
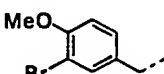
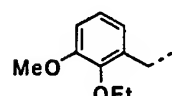
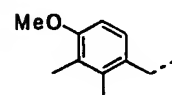
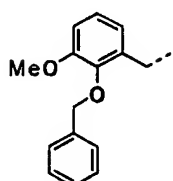
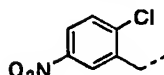
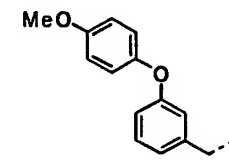
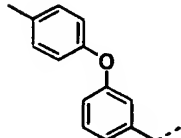
345

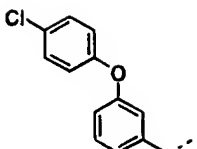
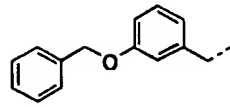
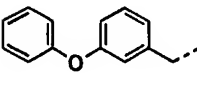
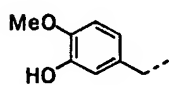
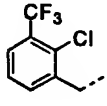
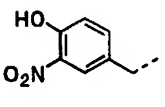
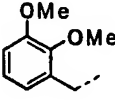
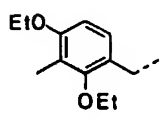
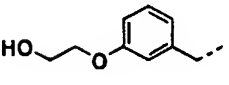
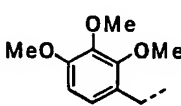
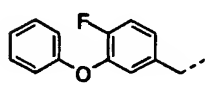
59		H	H	H	H	H	H
60		H	H	H	H	H	H
61		H	H	H	H	H	H
62		H	H	H	H	H	H
63		H	H	H	H	H	H
64		H	H	H	H	H	H
65		H	H	H	H	H	H
66		H	H	H	H	H	H
67		H	H	H	H	H	H
68		H	H	H	H	H	H
69		H	H	H	H	H	H
70		H	H	H	H	H	H

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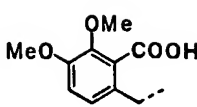
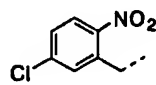
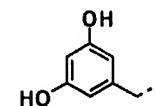
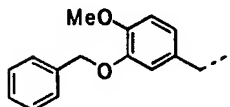
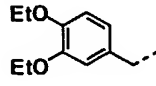
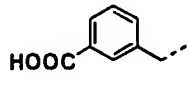
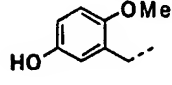
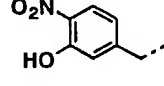
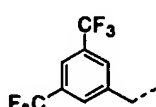
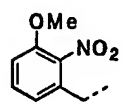
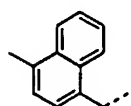
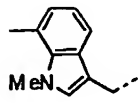
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75		H	H	H	H	H	H
76		H	H	H	H	H	H
77		H	H	H	H	H	H
78		H	H	H	H	H	H
79		H	H	H	H	H	H
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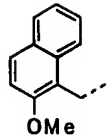
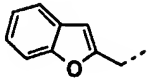
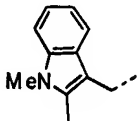
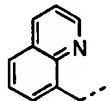
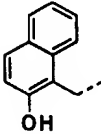
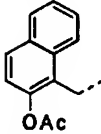
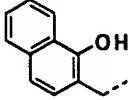
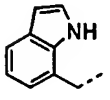
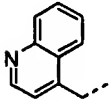
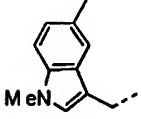
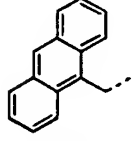
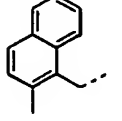
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87		H	H	H	H	H	H
88		H	H	H	H	H	H
89		H	H	H	H	H	H
90		H	H	H	H	H	H
91		H	H	H	H	H	H
92		H	H	H	H	H	H
93		H	H	H	H	H	H

94		H	H	H	H	H	H
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96		H	H	H	H	H	H
97		H	H	H	H	H	H
98		H	H	H	H	H	H
99		H	H	H	H	H	H
100		H	H	H	H	H	H
101		H	H	H	H	H	H
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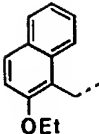
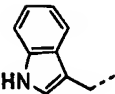
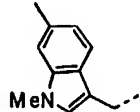
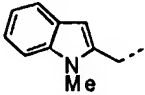
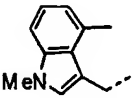
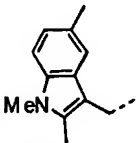
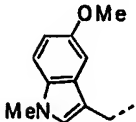
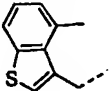
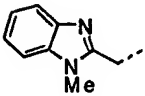
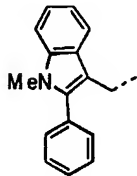
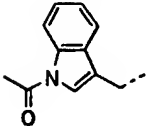
349

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110		H	H	H	H	H	H
111		H	H	H	H	H	H
112		H	H	H	H	H	H
113		H	H	H	H	H	H
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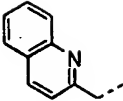
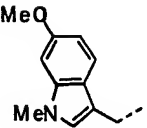
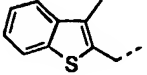
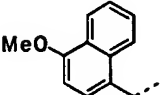
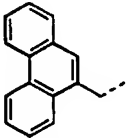
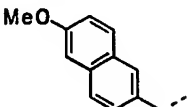
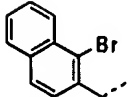
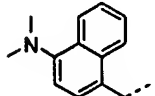
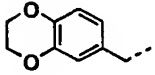
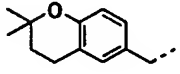
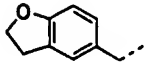
350

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121		H	H	H	H	H	H
122		H	H	H	H	H	H
123		H	H	H	H	H	H
124		H	H	H	H	H	H
125		H	H	H	H	H	H
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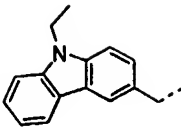
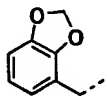
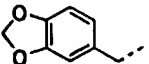
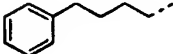
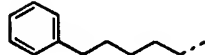

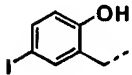
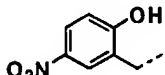
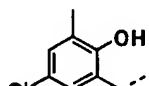
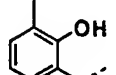
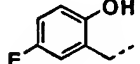
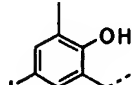
351

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135		H	H	H	H	H	H
136		H	H	H	H	H	H
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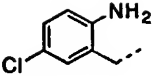

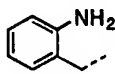
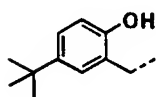
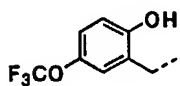
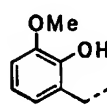
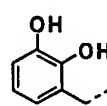
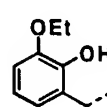
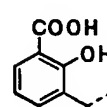
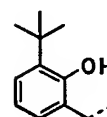
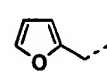
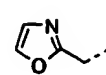
352

140		H	H	H	H	H	H
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146		H	H	H	H	H	H
147		H	H	H	H	H	H
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353




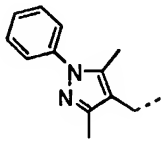
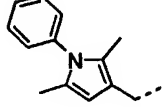
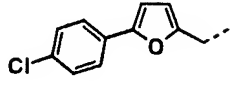





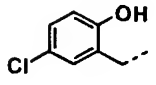
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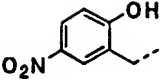
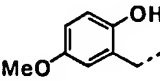
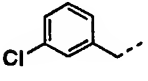
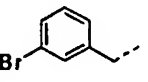
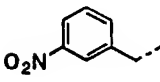
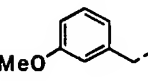
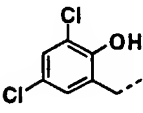
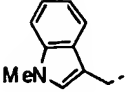
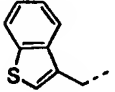
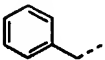
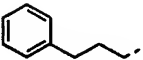
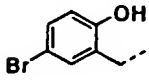
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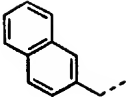
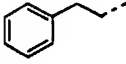
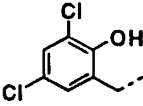
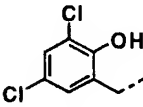
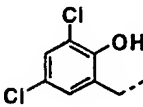
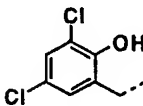
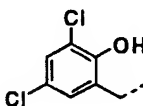
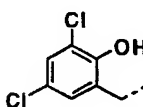
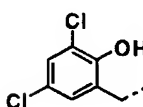
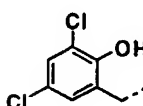
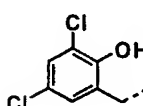
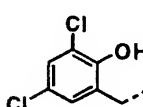
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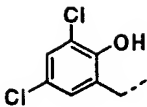
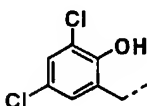
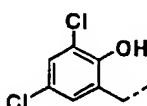
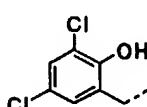
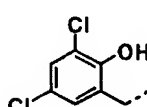
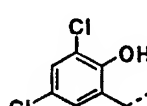
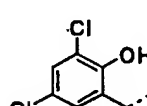
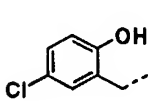
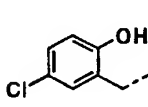
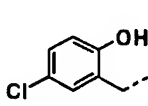
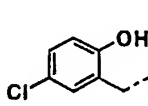
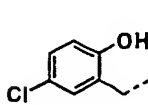
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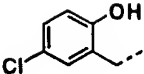
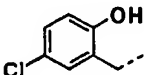
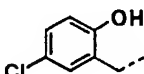
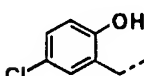
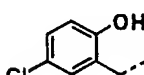
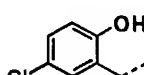
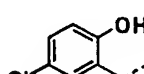
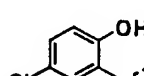
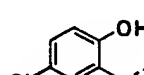
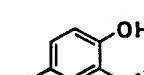
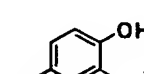
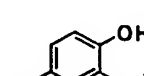
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357

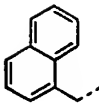
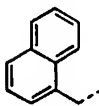
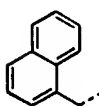
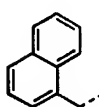
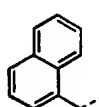
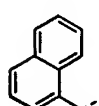
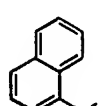
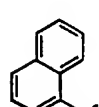
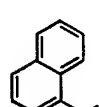
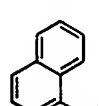
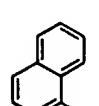
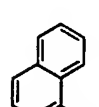
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204		H	H	H	H	Cl	H
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207		H	H	H	OCF3	H	H
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358

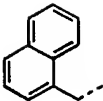
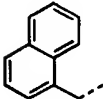
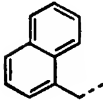
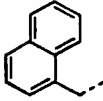
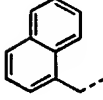
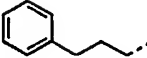
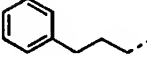
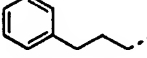
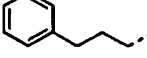
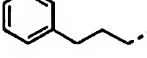
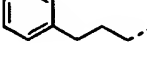
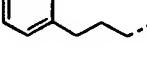
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216		H	H	Me	H	H	H
217		H	H	H	CN	H	H
218		H	H	Cl	H	H	H
219		H	H	H	OMe	H	H
220		H	H	H	COOMe	H	H
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222		H	H	H	H	COOMe	H

223		H	H	H	H	H	Cl
224		H	H	H	OCF3	H	H
225		H	H	COOMe	H	H	H
226		H	H	H	CF3	H	H
227		H	H	H	Me	H	H
228		H	H	H	F	H	H
229		H	H	H	OH	H	H
230		H	H	H	NO2	H	H
231		H	H	H	F	F	H
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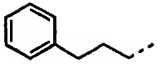
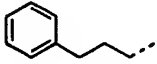
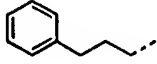
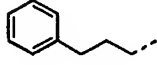
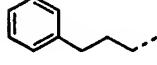
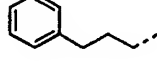
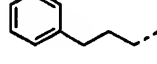
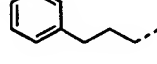
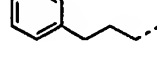
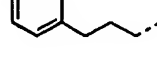
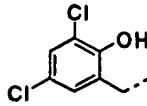
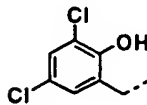
360

235		H	H	Cl	H	H	H
236		H	H	H	OMe	H	H
237		H	H	H	COOMe	H	H
238		H	H	H	H	Cl	H
239		H	H	H	H	COOMe	H
240		H	H	H	H	H	Cl
241		H	H	H	OCF3	H	H
242		H	H	COOMe	H	H	H
243		H	H	H	CF3	H	H
244		H	H	H	Me	H	H
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246		H	H	H	OH	H	H

361

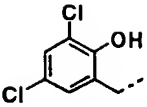
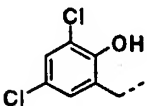
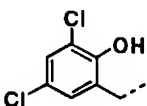
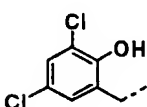
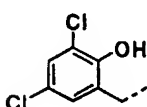
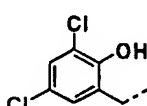
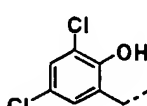
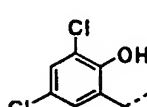
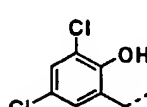
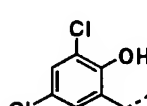
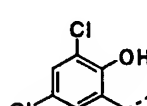
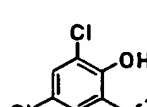
247		H	H	H	NO2	H	H
248		H	H	H	F	F	H
249		H	H	F	H	H	H
250		H	H	Me	H	H	H
251		H	H	H	CN	H	H
252		H	H	Cl	H	H	H
253		H	H	H	OMe	H	H
254		H	H	H	COOMe	H	H
255		H	H	H	H	Cl	H
256		H	H	H	H	COOMe	H
257		H	H	H	H	H	Cl
258		H	H	H	OCF3	H	H

362

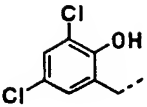
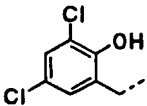
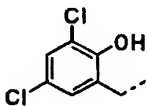
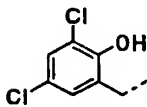
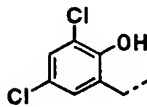
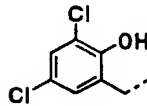
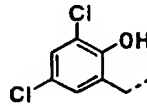
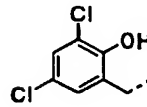
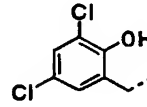
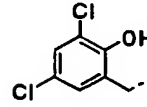
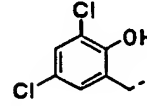
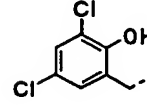
259		H	H	COOMe	H	H	H
260		H	H	H	CF3	H	H
261		H	H	H	Me	H	H
262		H	H	H	F	H	H
263		H	H	H	OH	H	H
264		H	H	H	NO2	H	H
265		H	H	H	F	F	H
266		H	H	F	H	H	H
267		H	H	Me	H	H	H
268		H	H	H	CN	H	H
269		H	H	H	H	H	COOMe
270		H	H	H	H	F	H



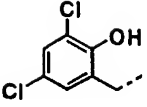
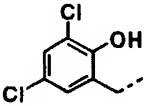
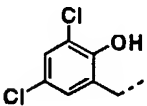
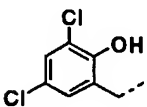
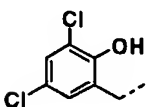
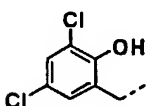
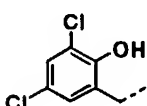
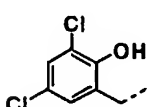
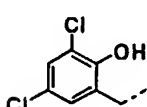
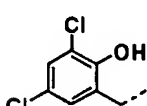
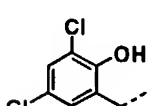
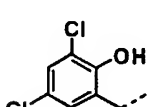
363

271		H	H	H	H	H	F
272		H	H	H	H	Me	H
273		H	H	H	H	H	Me
274		H	H	OMe	H	H	H
275		H	H	H	H	OMe	H
276		H	H	H	H	H	OMe
277		H	H	CF3	H	H	H
278		H	H	H	H	CF3	H
279		H	H	H	H	H	CF3
280		H	H	OH	H	H	H
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282		H	H	H	H	H	OH

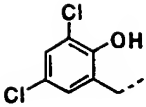
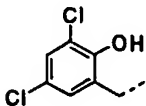
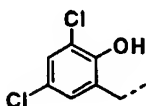
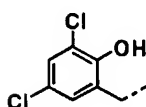
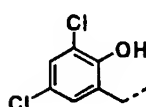
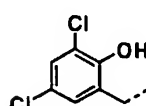
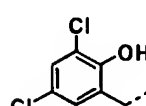
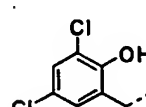
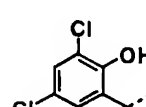
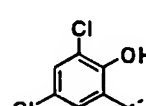
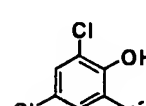
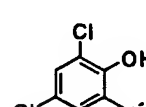
364

283		H	H	OCF3	H	H	H
284		H	H	H	H	OCF3	H
285		H	H	H	H	H	OCF3
286		H	H	NO2	H	H	H
287		H	H	H	H	NO2	H
288		H	H	H	H	H	NO2
289		H	H	CN	H	H	H
290		H	H	H	H	CN	H
291		H	H	H	H	H	CN
292		H	H	Br	H	H	H
293		H	H	H	Br	H	H
294		H	H	H	H	Br	H

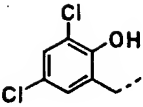
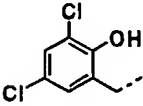
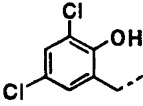
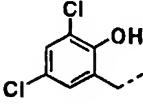
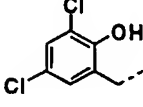
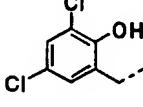
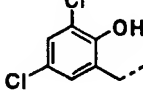
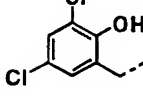
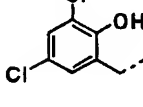
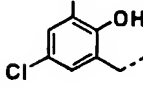
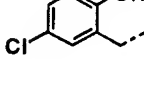
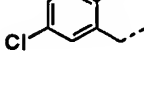
365

295		H	H	H	H	H	Br
296		H	H	COOH	H	H	H
297		H	H	H	COOH	H	H
298		H	H	H	H	COOH	H
299		H	H	H	H	H	COOH
300		H	H	NHCOMe	H	H	H
301		H	H	H	NHCOMe	H	H
302		H	H	H	H	NHCOMe	H
303		H	H	H	H	H	NHCOMe
304		H	H	SO2NH2	H	H	H
305		H	H	H	SO2NH2	H	H
306		H	H	H	H	SO2NH2	H

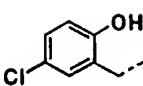
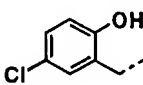
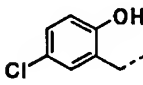
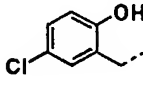
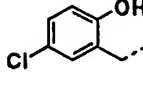
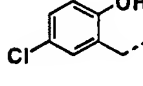
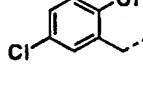
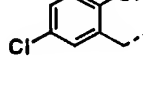
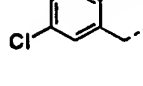
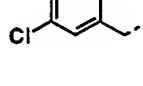
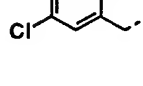
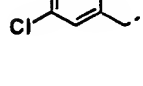
366

307		H	H	H	H	H	SO <sub>2</sub> NH <sub>2</sub>
308		H	H	Me	Me	H	H
309		H	H	Me	H	Me	H
310		H	H	H	Me	Me	H
311		H	H	F	F	H	H
312		H	H	F	H	F	H
313		H	H	H	F	F	H
314		H	H	Cl	Cl	H	H
315		H	H	Cl	H	Cl	H
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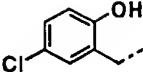
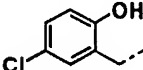
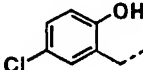
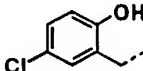
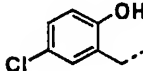
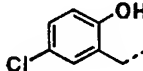
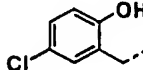
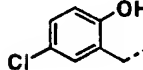
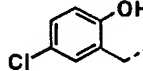
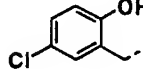
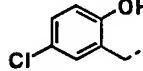
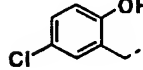
367

319		H	H	Me	OH	H	H
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321		H	H	F	Me	H	H
322		H	H	F	Cl	H	H
323		H	H	F	OH	H	H
324		H	H	F	OMe	H	H
325		H	H	Cl	Me	H	H
326		H	H	Cl	F	H	H
327		H	H	Cl	OH	H	H
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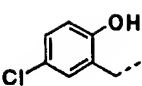
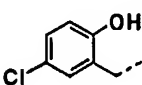
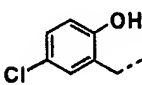
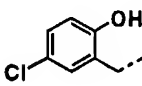
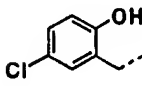
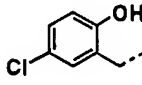
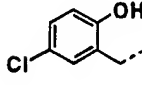
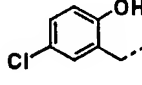
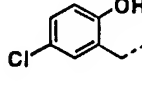
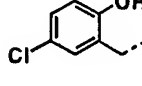
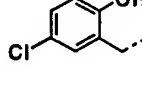
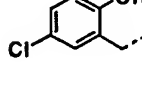
368

331		H	H	H	H	H	F
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333		H	H	H	H	H	Me
334		H	H	OMe	H	H	H
335		H	H	H	H	OMe	H
336		H	H	H	H	H	OMe
337		H	H	CF3	H	H	H
338		H	H	H	H	CF3	H
339		H	H	H	H	H	CF3
340		H	H	OH	H	H	H
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342		H	H	H	H	H	OH

369

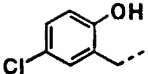
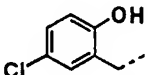
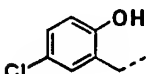
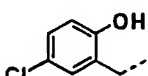
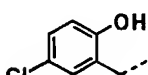
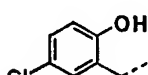
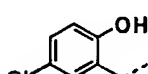
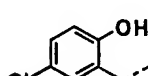
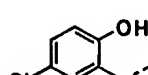
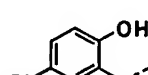
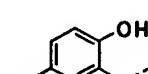
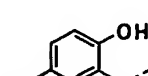
343		H	H	OCF3	H	H	H
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345		H	H	H	H	H	OCF3
346		H	H	NO2	H	H	H
347		H	H	H	H	NO2	H
348		H	H	H	H	H	NO2
349		H	H	CN	H	H	H
350		H	H	H	H	CN	H
351		H	H	H	H	H	CN
352		H	H	Br	H	H	H
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354		H	H	H	H	Br	H

370

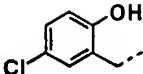
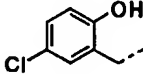
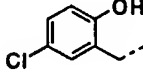
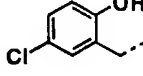
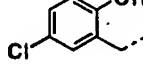
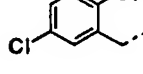
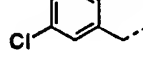
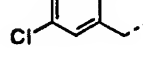
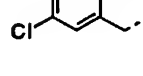
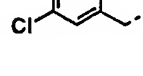
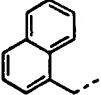
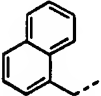
355		H	H	H	H	H	Br
356		H	H	COOH	H	H	H
357		H	H	H	COOH	H	H
358		H	H	H	H	COOH	H
359		H	H	H	H	H	COOH
360		H	H	NHCOMe	H	H	H
361		H	H	H	NHCOMe	H	H
362		H	H	H	H	NHCOMe	H
363		H	H	H	H	H	NHCOMe
364		H	H	SO2NH2	H	H	H
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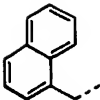
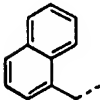
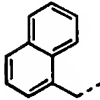
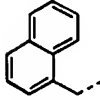
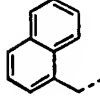
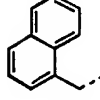
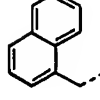
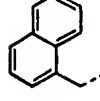
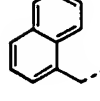
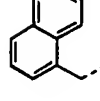
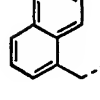
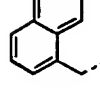
371

367		H	H	H	H	H	SO <sub>2</sub> NH <sub>2</sub>
368		H	H	Me	Me	H	H
369		H	H	Me	H	Me	H
370		H	H	H	Me	Me	H
371		H	H	F	F	H	H
372		H	H	F	H	F	H
373		H	H	H	F	F	H
374		H	H	Cl	Cl	H	H
375		H	H	Cl	H	Cl	H
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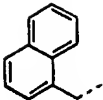
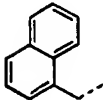
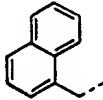
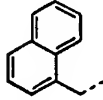
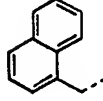
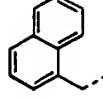
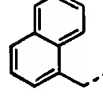
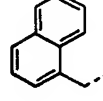
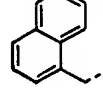
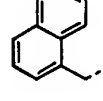
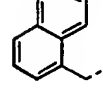
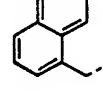
372

379		H	H	Me	OH	H	H
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383		H	H	F	OH	H	H
384		H	H	F	OMe	H	H
385		H	H	Cl	Me	H	H
386		H	H	Cl	F	H	H
387		H	H	Cl	OH	H	H
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389		H	H	H	H	H	COOMe
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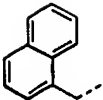
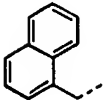
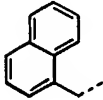
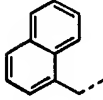
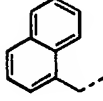
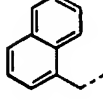
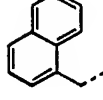
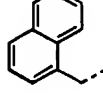
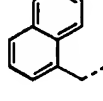
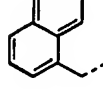
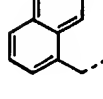
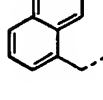
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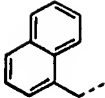
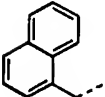
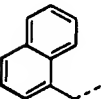
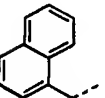
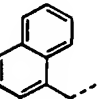
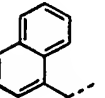
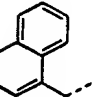
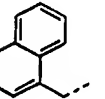
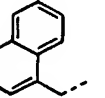
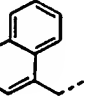
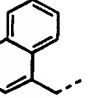
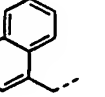
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394		H	H	OMe	H	H	H
395		H	H	H	H	OMe	H
396		H	H	H	H	H	OMe
397		H	H	CF3	H	H	H
398		H	H	H	H	CF3	H
399		H	H	H	H	H	CF3
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374

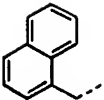
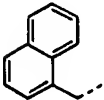
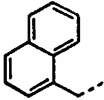
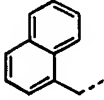
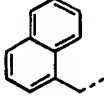
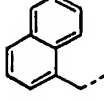
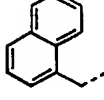
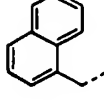
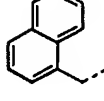
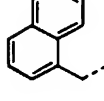
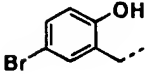
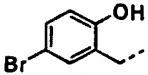
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406		H	H	NO2	H	H	H
407		H	H	H	H	NO2	H
408		H	H	H	H	H	NO2
409		H	H	CN	H	H	H
410		H	H	H	H	CN	H
411		H	H	H	H	H	CN
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375

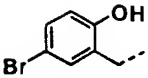
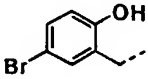
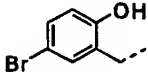
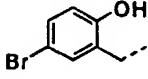
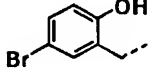
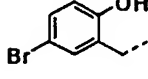
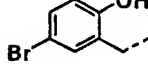
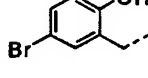
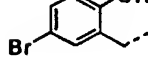
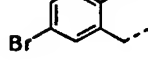
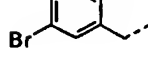
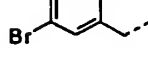
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419		H	H	H	H	H	COOH
420		H	H	NHCOMe	H	H	H
421		H	H	H	NHCOMe	H	H
422		H	H	H	H	NHCOMe	H
423		H	H	H	H	H	NHCOMe
424		H	H	SO <sub>2</sub> NH <sub>2</sub>	H	H	H
425		H	H	H	SO <sub>2</sub> NH <sub>2</sub>	H	H
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427		H	H	H	H	H	SO <sub>2</sub> NH <sub>2</sub>
428		H	H	Me	Me	H	H
429		H	H	Me	H	Me	H
430		H	H	H	Me	Me	H
431		H	H	F	F	H	H
432		H	H	F	H	F	H
433		H	H	H	F	F	H
434		H	H	Cl	Cl	H	H
435		H	H	Cl	H	Cl	H
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377

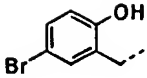
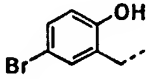
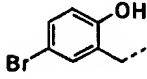
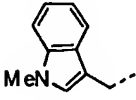
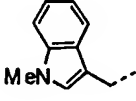
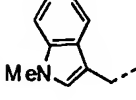
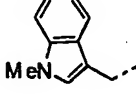
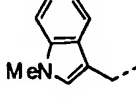
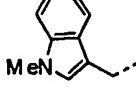
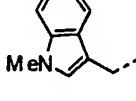
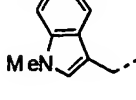
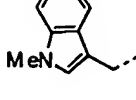
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444		H	H	F	OMe	H	H
445		H	H	Cl	Me	H	H
446		H	H	Cl	F	H	H
447		H	H	Cl	OH	H	H
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378

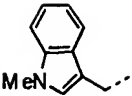
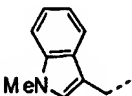
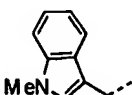
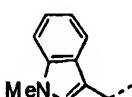
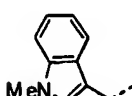
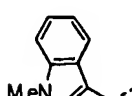
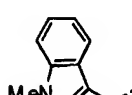
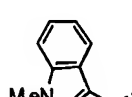
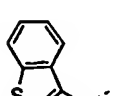
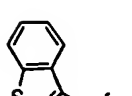
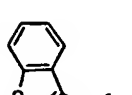
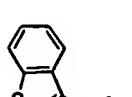
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455		H	H	H	OCF3	H	H
456		H	H	COOMe	H	H	H
457		H	H	H	CF3	H	H
458		H	H	H	Me	H	H
459		H	H	H	F	H	H
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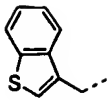
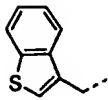
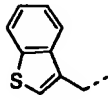
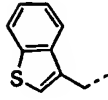
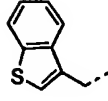
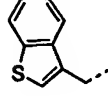
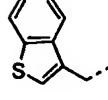
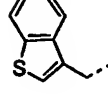
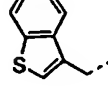
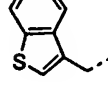
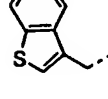
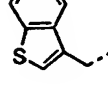
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467		H	H	H	OMe	H	H
468		H	H	H	COOMe	H	H
469		H	H	H	H	Cl	H
470		H	H	H	H	COOMe	H
471		H	H	H	H	H	Cl
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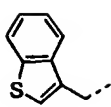
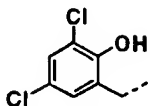
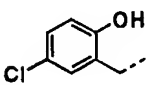
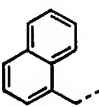
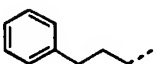
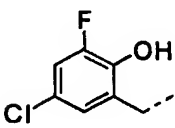
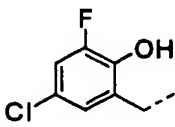
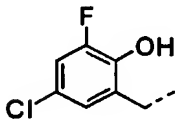
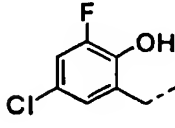
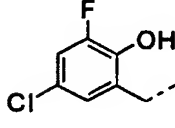
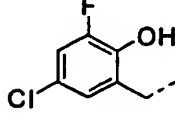
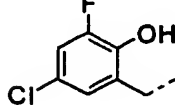
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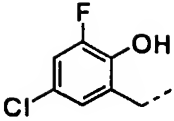
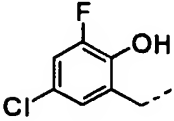
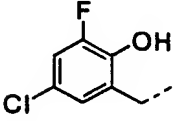
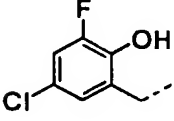
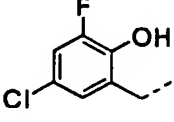
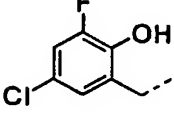
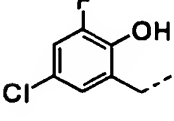
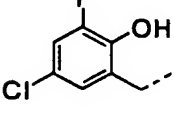
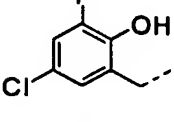
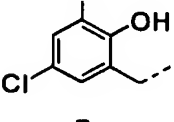
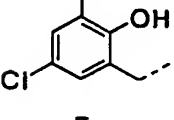
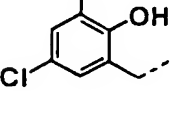
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478		H	H	H	NO <sub>2</sub>	H	H
479		H	H	H	F	F	H
480		H	H	F	H	H	H
481		H	H	Me	H	H	H
482		H	H	H	CN	H	H
483		H	H	Cl	H	H	H
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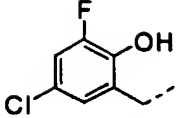
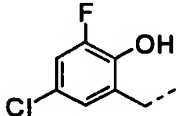
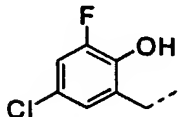
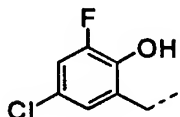
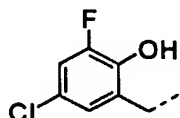
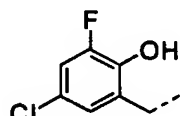
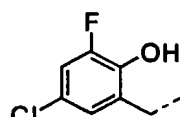
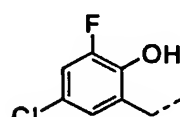
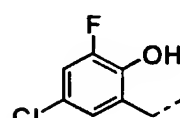
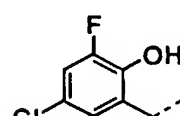
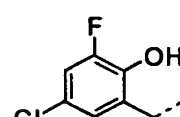
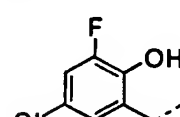
381

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491		H	H	H	CF3	H	H
492		H	H	H	Me	H	H
493		H	H	H	F	H	H
494		H	H	H	OH	H	H
495		H	H	H	NO2	H	H
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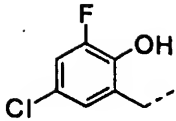
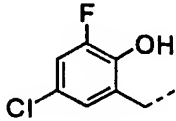
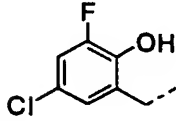
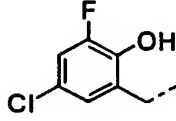
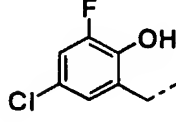
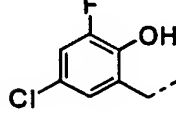
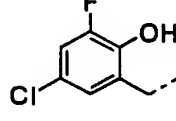
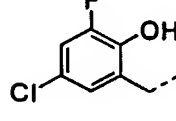
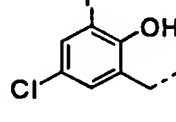
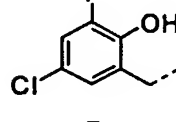
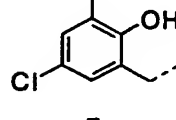
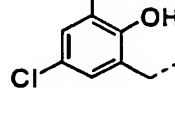
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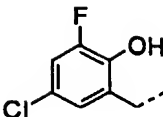
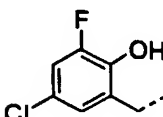
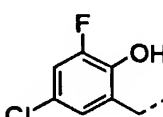
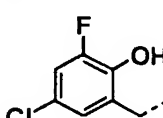
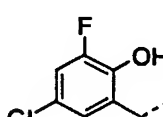
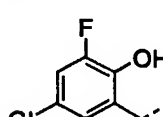
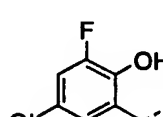
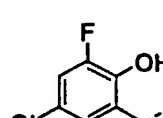
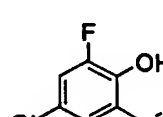
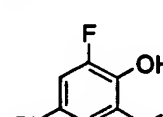
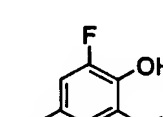
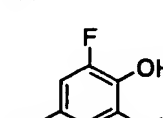
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504		H	H	H	H	H	H
505		H	H	F	H	H	H
506		H	H	Cl	H	H	H
507		H	H	Me	H	H	H
508		H	H	Et	H	H	H
509		H	H	OMe	H	H	H
510		H	H	OEt	H	H	H

511		H	H	CF3	H	H	H
512		H	H	OCF3	H	H	H
513		H	H	NO2	H	H	H
514		H	H	NH2	H	H	H
515		H	H	OH	H	H	H
516		H	H	CN	H	H	H
517		H	H	COMe	H	H	H
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519		H	H	H	F	H	H
520		H	H	H	Cl	H	H
521		H	H	H	Me	H	H
522		H	H	H	Et	H	H

523		H	H	H	OMe	H	H
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526		H	H	H	OCF3	H	H
527		H	H	H	NO2	H	H
528		H	H	H	NH2	H	H
529		H	H	H	OH	H	H
530		H	H	H	CN	H	H
531		H	H	H	COMe	H	H
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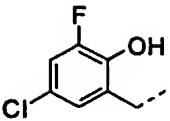
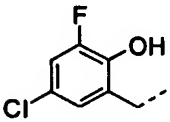
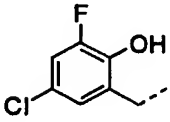
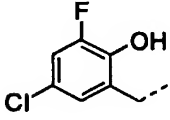
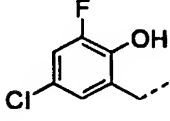
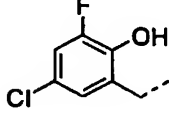
385

535		H	H	F	Me	H	H
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540		H	H	F	OCF3	H	H
541		H	H	Cl	F	H	H
542		H	H	Cl	Cl	H	H
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547		H	H	Cl	CF <sub>3</sub>	H	H
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549		H	H	Me	F	H	H
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553		H	H	Me	OMe	H	H
554		H	H	Me	OEt	H	H
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558		H	H	OMe	Cl	H	H

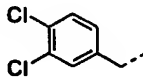
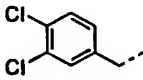
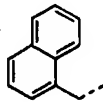
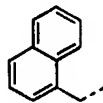
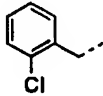
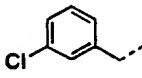
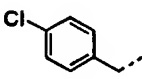
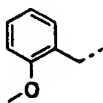
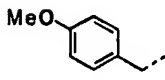
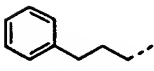


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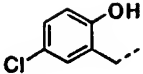
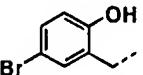
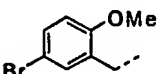
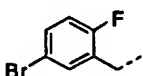
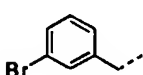
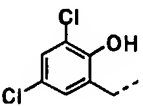
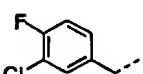
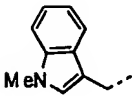
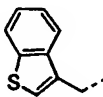
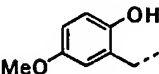
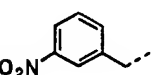
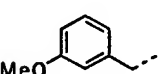
559		H	H	OMe	Me	H	H
560		H	H	OMe	Et	H	H
561		H	H	OMe	OMe	H	H
562		H	H	OMe	OEt	H	H
563		H	H	OMe	CF3	H	H
564		H	H	OMe	OCF3	H	H

$$X = -CS-, q = 0, r = 0, Y = -(R_4)C=C(R_5)-$$

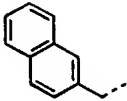
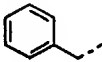
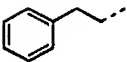
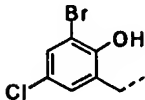
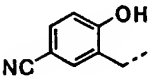
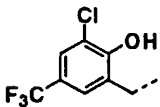
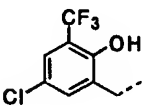
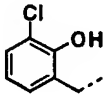
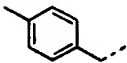
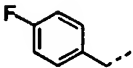
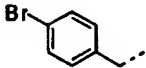
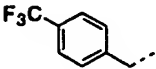
表 8

compnd NO.8-	R1-(CH <sub>2</sub> ) <sub>p</sub> -	R2	R3	R4	R5	R6	R7
1		H	H	H	H	H	H
2		H	H	H	Cl	H	H
3		H	H	H	H	H	H
4		H	H	H	Cl	H	H
5		H	H	H	H	H	H
6		H	H	H	H	H	H
7		H	H	H	H	H	H
8		H	H	H	H	H	H
9		H	H	H	H	H	H
10		H	H	H	H	H	H

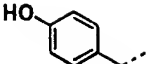
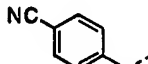
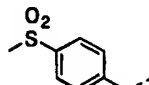
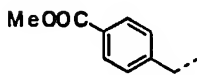
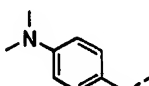
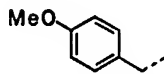
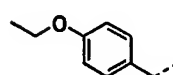
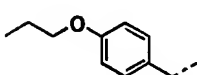
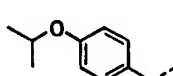
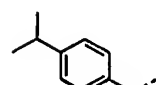
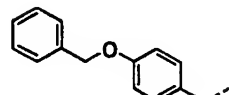
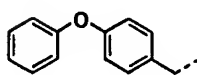
389

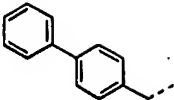
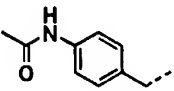
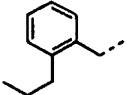
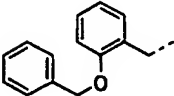
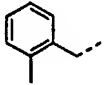
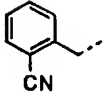
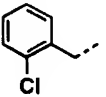
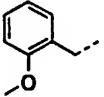
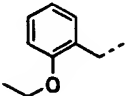
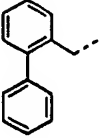
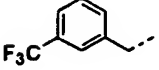
11		H	H	H	H	H	H
12		H	H	H	H	H	H
13		H	H	H	H	H	H
14		H	H	H	H	H	H
15		H	H	H	H	H	H
16		H	H	H	H	H	H
17		H	H	H	H	H	H
18		H	H	H	H	H	H
19		H	H	H	H	H	H
20		H	H	H	H	H	H
21		H	H	H	H	H	H
22		H	H	H	H	H	H

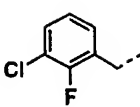
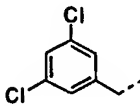
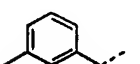
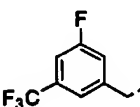
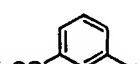
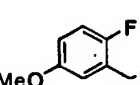
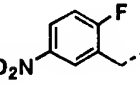
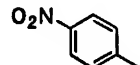
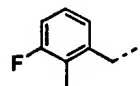
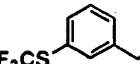
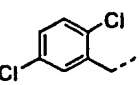
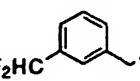
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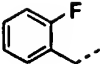
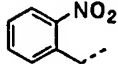
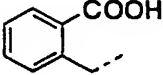
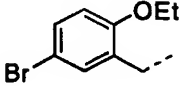
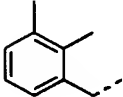
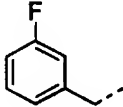
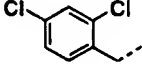
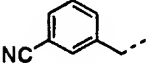
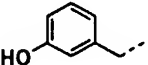
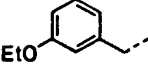
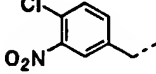
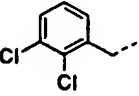
23		H	H	H	H	H	H
24		H	H	H	H	H	H
25		H	H	H	H	H	H
26		H	H	H	H	H	H
27		H	H	H	H	H	H
28		H	H	H	H	H	H
29		H	H	H	H	H	H
30		H	H	H	H	H	H
31		H	H	H	H	H	H
32		H	H	H	H	H	H
33		H	H	H	H	H	H
34		H	H	H	H	H	H

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35		H	H	H	H	H	H
36		H	H	H	H	H	H
37		H	H	H	H	H	H
38		H	H	H	H	H	H
39		H	H	H	H	H	H
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41		H	H	H	H	H	H
42		H	H	H	H	H	H
43		H	H	H	H	H	H
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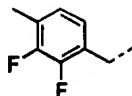
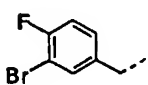
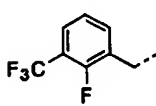
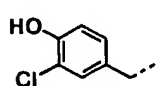
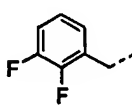
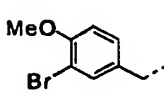
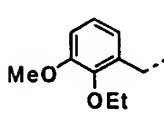
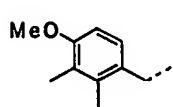
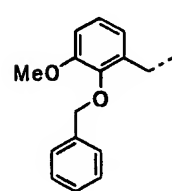
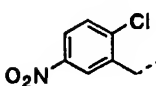
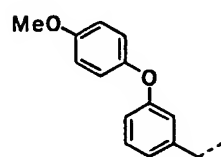
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55		H	H	H	H	H	H
56		H	H	H	H	H	H
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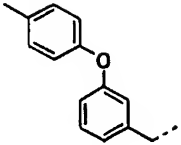
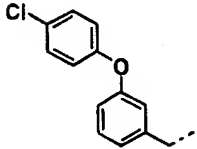
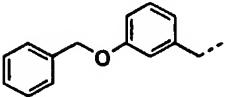
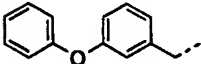
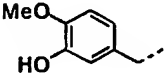
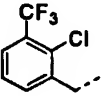
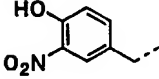
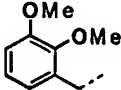
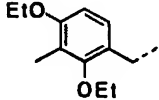
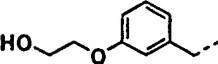
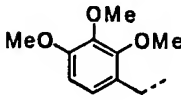
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76		H	H	H	H	H	H
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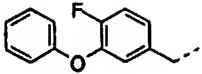
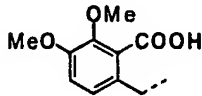
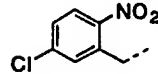
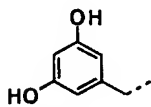
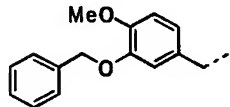
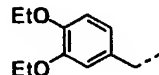
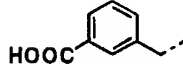
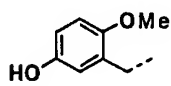
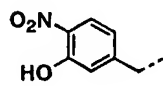
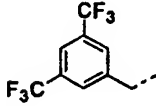
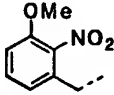
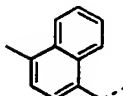


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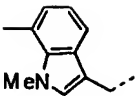
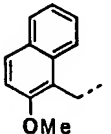
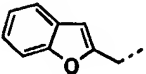
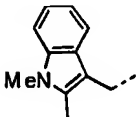
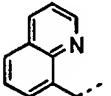
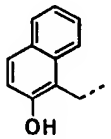
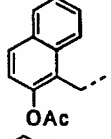
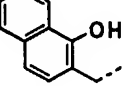
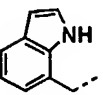
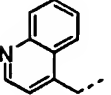
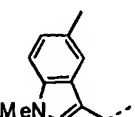
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88		H	H	H	H	H	H
89		H	H	H	H	H	H
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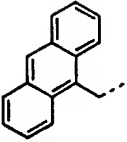
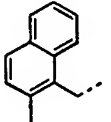
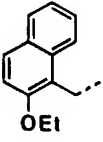
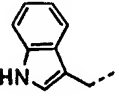
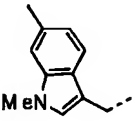
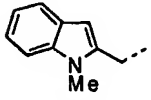
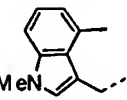
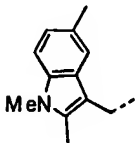
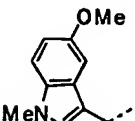
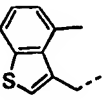
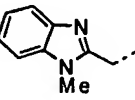
396

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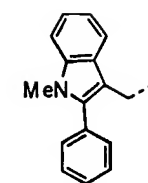
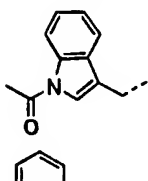
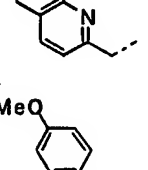
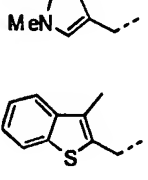
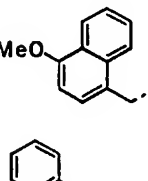
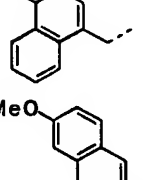
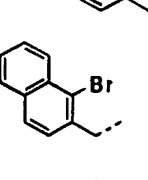
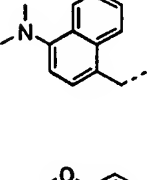
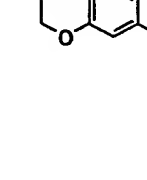

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398

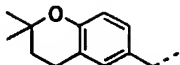
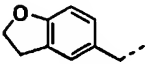
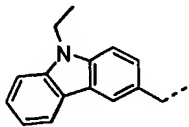
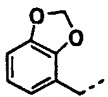
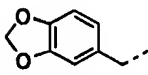
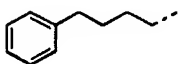
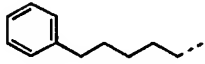
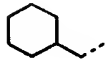
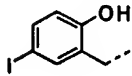
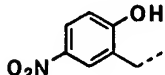
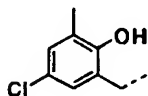
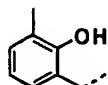
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126		H	H	H	H	H	H

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134		H	H	H	H	H	H
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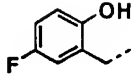
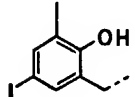
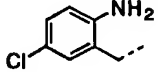
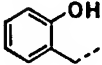
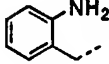
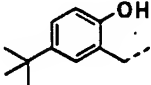
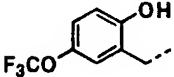
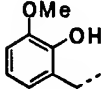
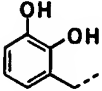
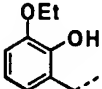
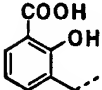
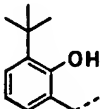
400

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142		H	H	H	H	H	H
143		H	H	H	H	H	H
144		H	H	H	H	H	H
145		H	H	H	H	H	H
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401





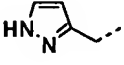
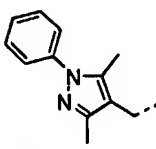
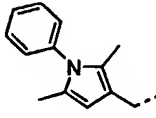
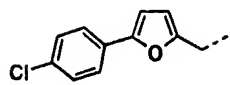




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153		H	H	H	H	H	H
154		H	H	H	H	H	H
155		H	H	H	H	H	H
156		H	H	H	H	H	H
157		H	H	H	H	H	H
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402

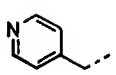
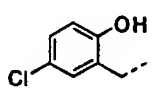
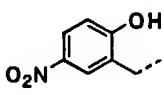
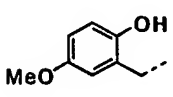
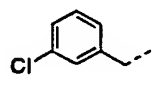
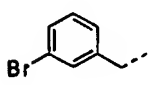
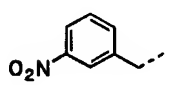
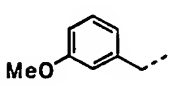
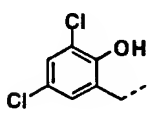
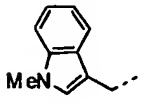
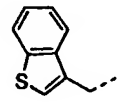
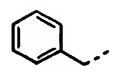
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165		H	H	H	H	H	H
166		H	H	H	H	H	H
167		H	H	H	H	H	H
168		H	H	H	H	H	H
169		H	H	H	H	H	H
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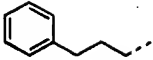
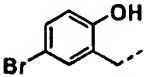
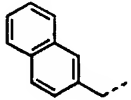
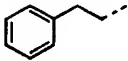
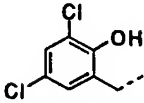
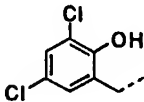
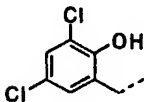
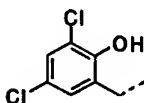
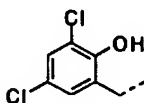
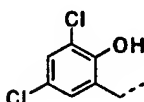
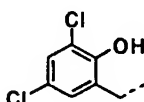
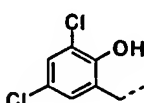
403

173		H	H	H	H	H	H
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176		H	H	H	H	H	H
177		H	H	H	H	H	H
178		H	H	H	H	H	H
179		H	H	H	H	H	H
180		H	H	H	H	H	H
181		H	H	H	H	H	H
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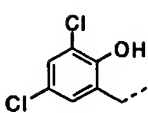
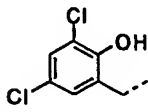
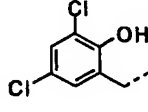
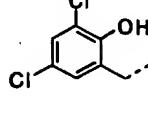
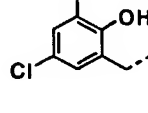
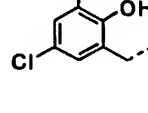
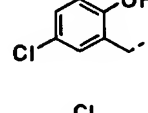
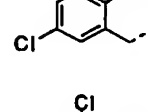
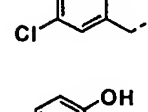
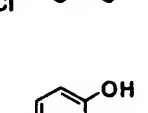
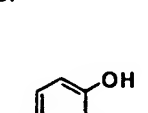

404

185		H	H	H	H	H	H
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187		H	H	H	Cl	H	H
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189		H	H	H	Cl	H	H
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191		H	H	H	Cl	H	H
192		H	H	H	Cl	H	H
193		H	H	H	Cl	H	H
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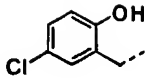
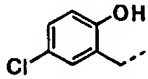
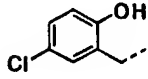
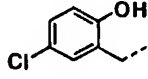
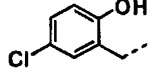
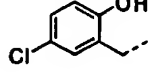
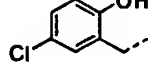
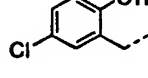
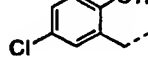
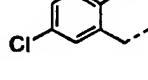
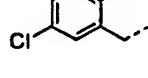
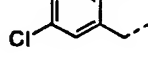
405

197		H	H	H	Cl	H	H
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201		H	H	Cl	H	H	H
202		H	H	H	OMe	H	H
203		H	H	H	COOMe	H	H
204		H	H	H	H	Cl	H
205		H	H	H	H	COOMe	H
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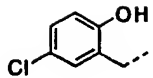
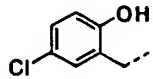
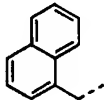
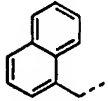
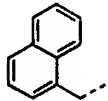
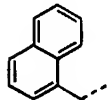
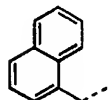
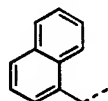
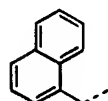
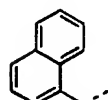
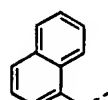
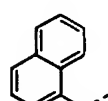
406

209		H	H	H	CF3	H	H
210		H	H	H	Me	H	H
211		H	H	H	F	H	H
212		H	H	H	OH	H	H
213		H	H	H	NO2	H	H
214		H	H	H	F	F	H
215		H	H	F	H	H	H
216		H	H	Me	H	H	H
217		H	H	H	CN	H	H
218		H	H	Cl	H	H	H
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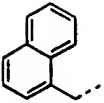
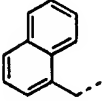
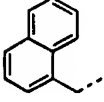
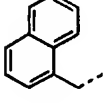
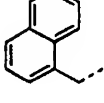
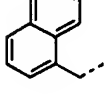
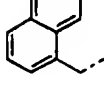

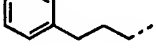
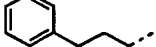
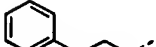

407

221		H	H	H	H	Cl	H
222		H	H	H	H	COOMe	H
223		H	H	H	H	H	Cl
224		H	H	H	OCF3	H	H
225		H	H	COOMe	H	H	H
226		H	H	H	CF3	H	H
227		H	H	H	Me	H	H
228		H	H	H	F	H	H
229		H	H	H	OH	H	H
230		H	H	H	NO2	H	H
231		H	H	H	F	F	H
232		H	H	F	H	H	H

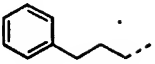
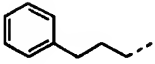
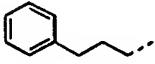
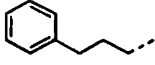
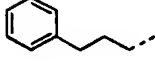
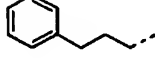
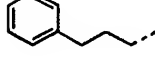
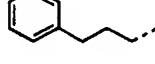
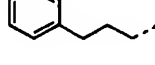
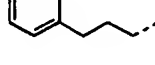
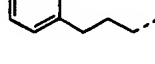
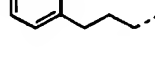
408

233		H	H	Me	H	H	H
234		H	H	H	CN	H	H
235		H	H	Cl	H	H	H
236		H	H	H	OMe	H	H
237		H	H	H	COOMe	H	H
238		H	H	H	H	Cl	H
239		H	H	H	H	COOMe	H
240		H	H	H	H	H	Cl
241		H	H	H	OCF3	H	H
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244		H	H	H	Me	H	H

409

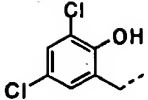
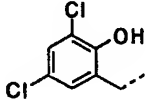
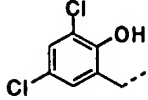
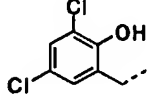
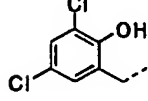
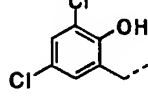
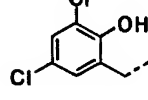
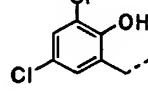
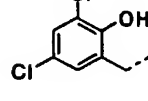
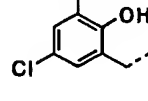
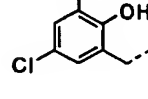
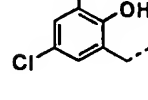
245		H	H	H	F	H	H
246		H	H	H	OH	H	H
247		H	H	H	NO2	H	H
248		H	H	H	F	F	H
249		H	H	F	H	H	H
250		H	H	Me	H	H	H
251		H	H	H	CN	H	H
252		H	H	Cl	H	H	H
253		H	H	H	OMe	H	H
254		H	H	H	COOMe	H	H
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256		H	H	H	H	COOMe	H

410

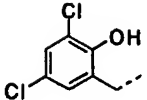
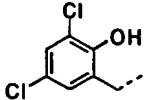
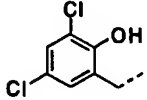
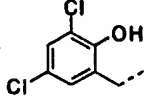
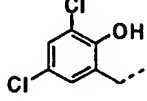
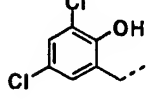
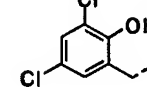
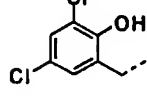
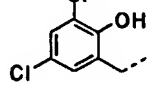
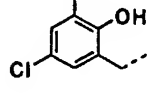
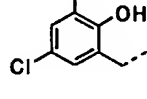
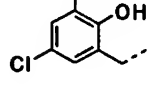
257		H	H	H	H	H	Cl
258		H	H	H	OCF3	H	H
259		H	H	COOMe	H	H	H
260		H	H	H	CF3	H	H
261		H	H	H	Me	H	H
262		H	H	H	F	H	H
263		H	H	H	OH	H	H
264		H	H	H	NO2	H	H
265		H	H	H	F	F	H
266		H	H	F	H	H	H
267		H	H	Me	H	H	H
268		H	H	H	CN	H	H



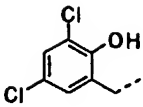
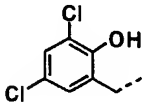
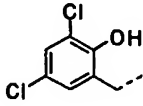
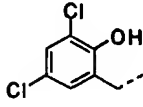
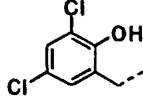
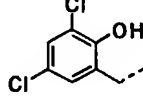
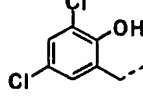
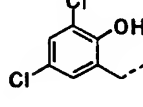
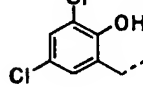
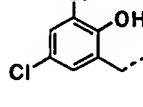
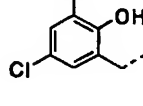
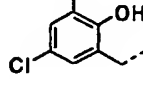
411

269		H	H	H	H	H	COOMe
270		H	H	H	H	F	H
271		H	H	H	H	H	F
272		H	H	H	H	Me	H
273		H	H	H	H	H	Me
274		H	H	OMe	H	H	H
275		H	H	H	H	OMe	H
276		H	H	H	H	H	OMe
277		H	H	CF3	H	H	H
278		H	H	H	H	CF3	H
279		H	H	H	H	H	CF3
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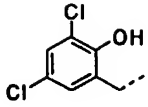
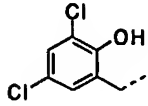
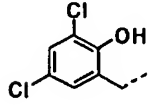
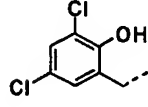
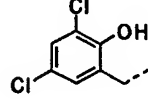
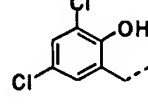
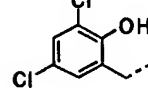
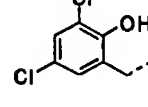
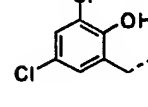
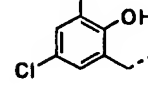
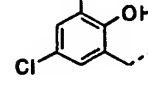
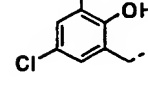
412

281		H	H	H	H	OH	H
282		H	H	H	H	H	OH
283		H	H	OCF3	H	H	H
284		H	H	H	H	OCF3	H
285		H	H	H	H	H	OCF3
286		H	H	NO2	H	H	H
287		H	H	H	H	NO2	H
288		H	H	H	H	H	NO2
289		H	H	CN	H	H	H
290		H	H	H	H	CN	H
291		H	H	H	H	H	CN
292		H	H	Br	H	H	H

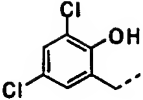
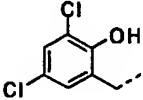
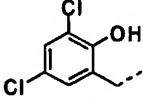
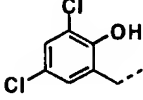
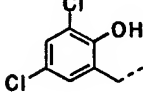
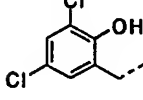
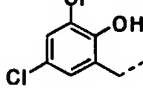
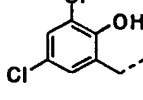
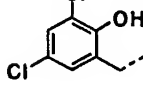
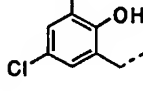
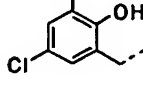
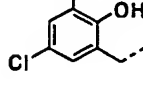
413

293		H	H	H	Br	H	H
294		H	H	H	H	Br	H
295		H	H	H	H	H	Br
296		H	H	COOH	H	H	H
297		H	H	H	COOH	H	H
298		H	H	H	H	COOH	H
299		H	H	H	H	H	COOH
300		H	H	NHCOMe	H	H	H
301		H	H	H	NHCOMe	H	H
302		H	H	H	H	NHCOMe	H
303		H	H	H	H	H	NHCOMe
304		H	H	SO <sub>2</sub> NH <sub>2</sub>	H	H	H

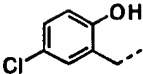
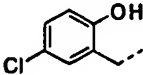
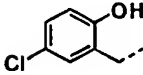
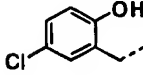
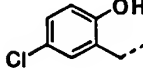
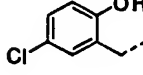
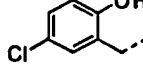
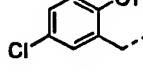
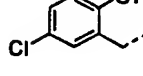
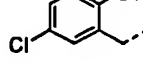
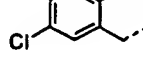
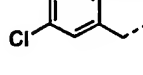
414

305		H	H	H	SO <sub>2</sub> NH <sub>2</sub>	H	H
306		H	H	H	H	SO <sub>2</sub> NH <sub>2</sub>	H
307		H	H	H	H	H	SO <sub>2</sub> NH <sub>2</sub>
308		H	H	Me	Me	H	H
309		H	H	Me	H	Me	H
310		H	H	H	Me	Me	H
311		H	H	F	F	H	H
312		H	H	F	H	F	H
313		H	H	H	F	F	H
314		H	H	Cl	Cl	H	H
315		H	H	Cl	H	Cl	H
316		H	H	H	Cl	Cl	H

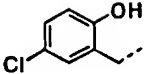
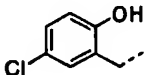
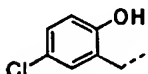
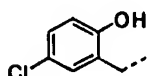
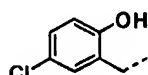
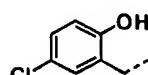
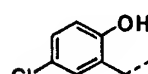
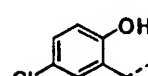
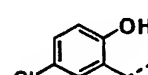
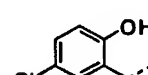
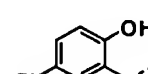
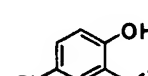
415

317		H	H	Me	F	H	H
318		H	H	Me	Cl	H	H
319		H	H	Me	OH	H	H
320		H	H	Me	OMe	H	H
321		H	H	F	Me	H	H
322		H	H	F	Cl	H	H
323		H	H	F	OH	H	H
324		H	H	F	OMe	H	H
325		H	H	Cl	Me	H	H
326		H	H	Cl	F	H	H
327		H	H	Cl	OH	H	H
328		H	H	Cl	OMe	H	H

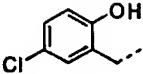
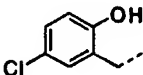
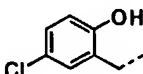
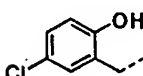
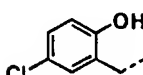
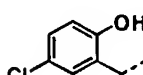
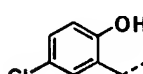
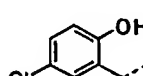
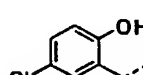
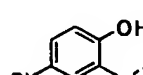
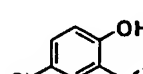
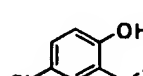
416

329		H	H	H	H	H	COOMe
330		H	H	H	H	F	H
331		H	H	H	H	H	F
332		H	H	H	H	Me	H
333		H	H	H	H	H	Me
334		H	H	OMe	H	H	H
335		H	H	H	H	OMe	H
336		H	H	H	H	H	OMe
337		H	H	CF3	H	H	H
338		H	H	H	H	CF3	H
339		H	H	H	H	H	CF3
340		H	H	OH	H	H	H

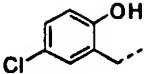
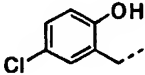
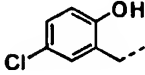
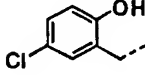
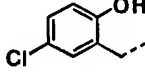
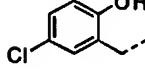
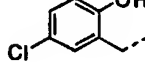
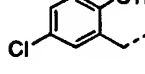
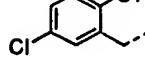
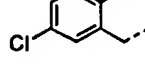
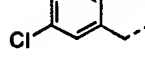
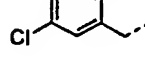
417

341		H	H	H	H	OH	H
342		H	H	H	H	H	OH
343		H	H	OCF3	H	H	H
344		H	H	H	H	OCF3	H
345		H	H	H	H	H	OCF3
346		H	H	NO2	H	H	H
347		H	H	H	H	NO2	H
348		H	H	H	H	H	NO2
349		H	H	CN	H	H	H
350		H	H	H	H	CN	H
351		H	H	H	H	H	CN
352		H	H	Br	H	H	H

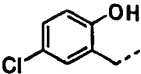
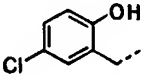
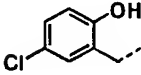
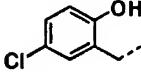
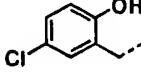
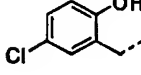
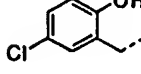
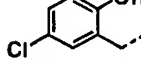
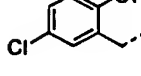
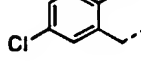
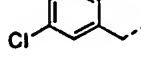
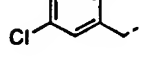
418

353		H	H	H	Br	H	H
354		H	H	H	H	Br	H
355		H	H	H	H	H	Br
356		H	H	COOH	H	H	H
357		H	H	H	COOH	H	H
358		H	H	H	H	COOH	H
359		H	H	H	H	H	COOH
360		H	H	NHCOMe	H	H	H
361		H	H	H	NHCOMe	H	H
362		H	H	H	H	NHCOMe	H
363		H	H	H	H	H	NHCOMe
364		H	H	SO <sub>2</sub> NH <sub>2</sub>	H	H	H

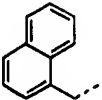
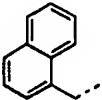
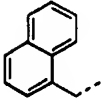
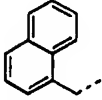
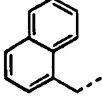
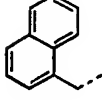
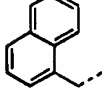
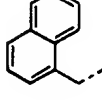
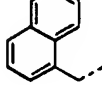
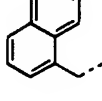
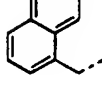
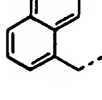


365		H	H	H	SO2NH2	H	H
366		H	H	H	H	SO2NH2	H
367		H	H	H	H	H	SO2NH2
368		H	H	Me	Me	H	H
369		H	H	Me	H	Me	H
370		H	H	H	Me	Me	H
371		H	H	F	F	H	H
372		H	H	F	H	F	H
373		H	H	H	F	F	H
374		H	H	Cl	Cl	H	H
375		H	H	Cl	H	Cl	H
376		H	H	H	Cl	Cl	H

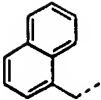
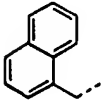
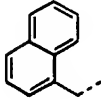
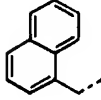
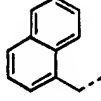
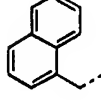
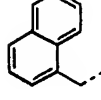
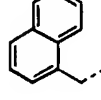
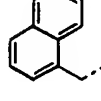
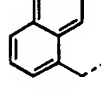
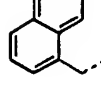
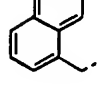
420

377		H	H	Me	F	H	H
378		H	H	Me	Cl	H	H
379		H	H	Me	OH	H	H
380		H	H	Me	OMe	H	H
381		H	H	F	Me	H	H
382		H	H	F	Cl	H	H
383		H	H	F	OH	H	H
384		H	H	F	OMe	H	H
385		H	H	Cl	Me	H	H
386		H	H	Cl	F	H	H
387		H	H	Cl	OH	H	H
388		H	H	Cl	OMe	H	H

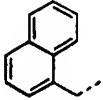
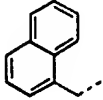
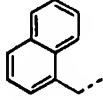
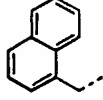
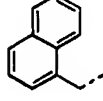
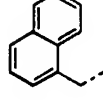
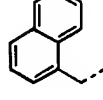
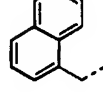
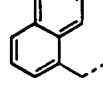
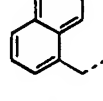
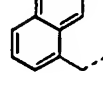
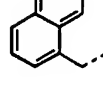
421

389		H	H	H	H	H	COOMe
390		H	H	H	H	F	H
391		H	H	H	H	H	F
392		H	H	H	H	Me	H
393		H	H	H	H	H	Me
394		H	H	OMe	H	H	H
395		H	H	H	H	OMe	H
396		H	H	H	H	H	OMe
397		H	H	CF3	H	H	H
398		H	H	H	H	CF3	H
399		H	H	H	H	H	CF3
400		H	H	OH	H	H	H

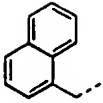
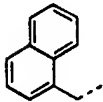
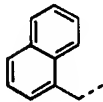
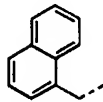
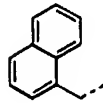
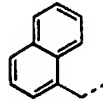
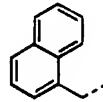
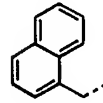
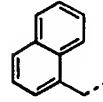
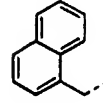
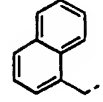
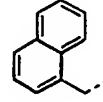
422

401		H	H	H	H	OH	H
402		H	H	H	H	H	OH
403		H	H	OCF3	H	H	H
404		H	H	H	H	OCF3	H
405		H	H	H	H	H	OCF3
406		H	H	NO2	H	H	H
407		H	H	H	H	NO2	H
408		H	H	H	H	H	NO2
409		H	H	CN	H	H	H
410		H	H	H	H	CN	H
411		H	H	H	H	H	CN
412		H	H	Br	H	H	H

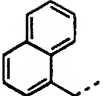
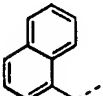
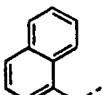
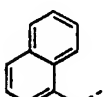
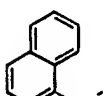
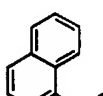
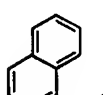
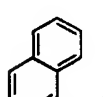
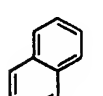
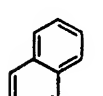
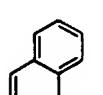
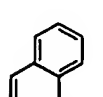
## 423

413		H	H	H	Br	H	H
414		H	H	H	H	Br	H
415		H	H	H	H	H	Br
416		H	H	COOH	H	H	H
417		H	H	H	COOH	H	H
418		H	H	H	H	COOH	H
419		H	H	H	H	H	COOH
420		H	H	NHCOMe	H	H	H
421		H	H	H	NHCOMe	H	H
422		H	H	H	H	NHCOMe	H
423		H	H	H	H	H	NHCOMe
424		H	H	SO <sub>2</sub> NH <sub>2</sub>	H	H	H

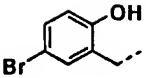
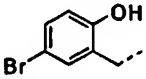
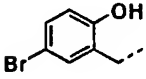
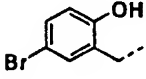
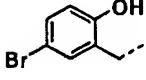
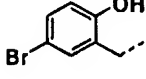
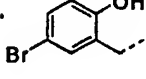
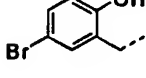
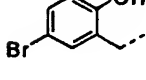
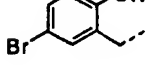
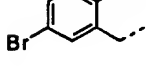
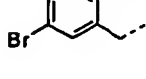
424

425		H	H	H	SO <sub>2</sub> NH <sub>2</sub>	H	H
426		H	H	H	H	SO <sub>2</sub> NH <sub>2</sub>	H
427		H	H	H	H	H	SO <sub>2</sub> NH <sub>2</sub>
428		H	H	Me	Me	H	H
429		H	H	Me	H	Me	H
430		H	H	H	Me	Me	H
431		H	H	F	F	H	H
432		H	H	F	H	F	H
433		H	H	H	F	F	H
434		H	H	Cl	Cl	H	H
435		H	H	Cl	H	Cl	H
436		H	H	H	Cl	Cl	H

425

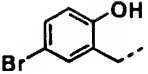
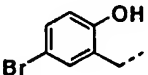
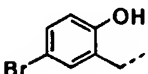
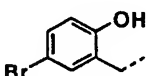
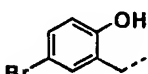
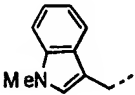
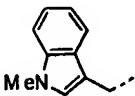
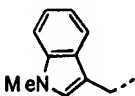
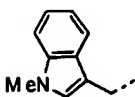
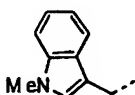
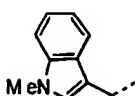
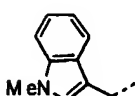
437		H	H	Me	F	H	H
438		H	H	Me	Cl	H	H
439		H	H	Me	OH	H	H
440		H	H	Me	OMe	H	H
441		H	H	F	Me	H	H
442		H	H	F	Cl	H	H
443		H	H	F	OH	H	H
444		H	H	F	OMe	H	H
445		H	H	Cl	Me	H	H
446		H	H	Cl	F	H	H
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448		H	H	Cl	OMe	H	H

426

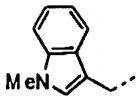
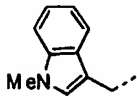
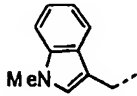
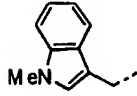
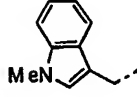
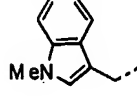
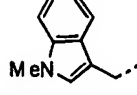
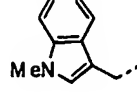
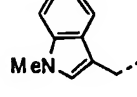
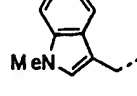
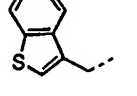
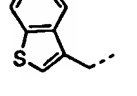
449		H	H	Cl	H	H	H
450		H	H	H	OMe	H	H
451		H	H	H	COOMe	H	H
452		H	H	H	H	Cl	H
453		H	H	H	H	COOMe	H
454		H	H	H	H	H	Cl
455		H	H	H	OCF3	H	H
456		H	H	COOMe	H	H	H
457		H	H	H	CF3	H	H
458		H	H	H	Me	H	H
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460		H	H	H	OH	H	H



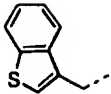
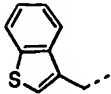
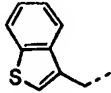
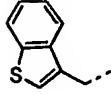
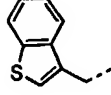
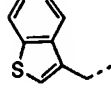
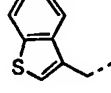
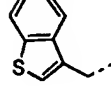
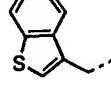
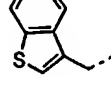
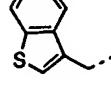
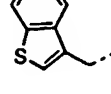
427

461		H	H	H	NO <sub>2</sub>	H	H
462		H	H	H	F	F	H
463		H	H	F	H	H	H
464		H	H	Me	H	H	H
465		H	H	H	CN	H	H
466		H	H	Cl	H	H	H
467		H	H	H	OMe	H	H
468		H	H	H	COOMe	H	H
469		H	H	H	H	Cl	H
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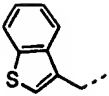
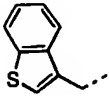
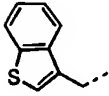
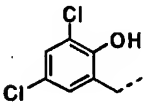
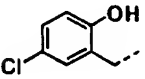
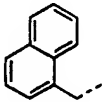
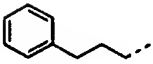
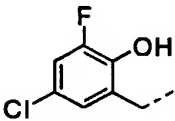
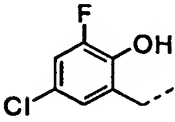
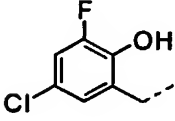
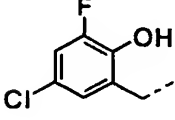
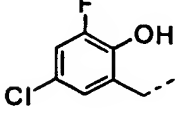
428

473		H	H	COOMe	H	H	H
474		H	H	H	CF3	H	H
475		H	H	H	Me	H	H
476		H	H	H	F	H	H
477		H	H	H	OH	H	H
478		H	H	H	NO2	H	H
479		H	H	H	F	F	H
480		H	H	F	H	H	H
481		H	H	Me	H	H	H
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483		H	H	Cl	H	H	H
484		H	H	H	OMe	H	H

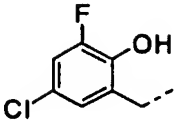
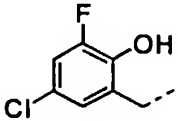
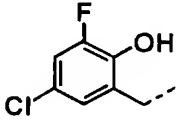
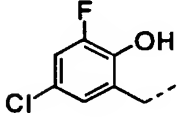
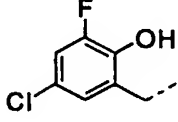
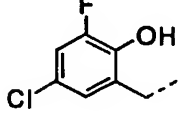
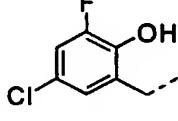
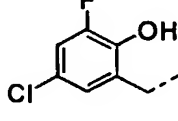
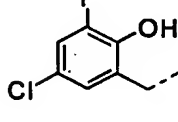
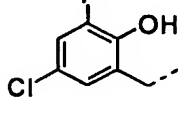
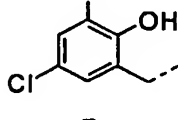
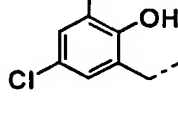
429

485		H	H	H	COOMe	H	H
486		H	H	H	H	Cl	H
487		H	H	H	H	COOMe	H
488		H	H	H	H	H	Cl
489		H	H	H	OCF3	H	H
490		H	H	COOMe	H	H	H
491		H	H	H	CF3	H	H
492		H	H	H	Me	H	H
493		H	H	H	F	H	H
494		H	H	H	OH	H	H
495		H	H	H	NO2	H	H
496		H	H	H	F	F	H

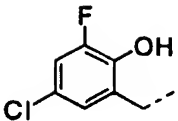
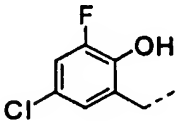
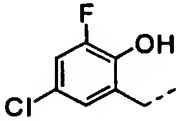
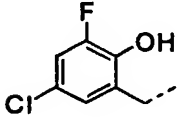
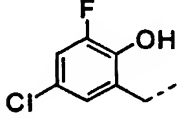
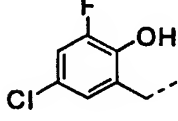
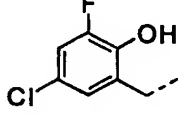
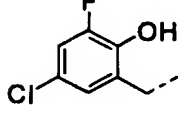
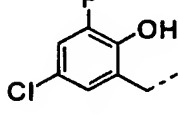
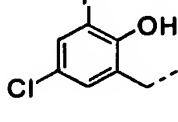
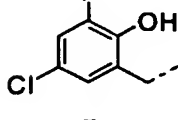
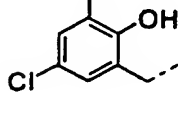
430

497		H	H	F	H	H	H
498		H	H	Me	H	H	H
499		H	H	H	CN	H	H
500		H	Me	H	H	H	H
501		H	Me	H	H	H	H
502		H	Me	H	H	H	H
503		H	Me	H	H	H	H
504		H	H	H	H	H	H
505		H	H	F	H	H	H
506		H	H	Cl	H	H	H
507		H	H	Me	H	H	H
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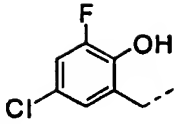
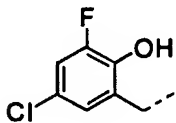
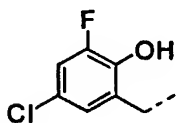
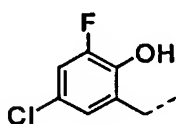
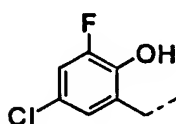
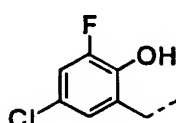
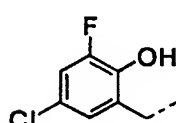
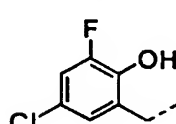
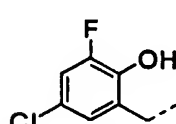
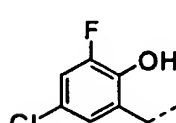
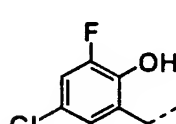
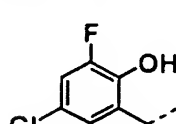
431

509		H	H	OMe	H	H	H
510		H	H	OEt	H	H	H
511		H	H	CF3	H	H	H
512		H	H	OCF3	H	H	H
513		H	H	NO2	H	H	H
514		H	H	NH2	H	H	H
515		H	H	OH	H	H	H
516		H	H	CN	H	H	H
517		H	H	COMe	H	H	H
518		H	H	COOMe	H	H	H
519		H	H	H	F	H	H
520		H	H	H	Cl	H	H

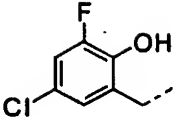
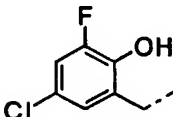
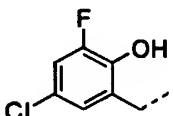
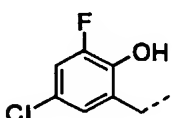
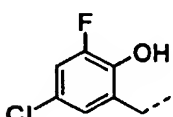
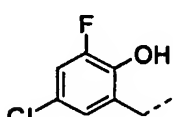
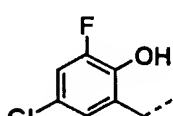
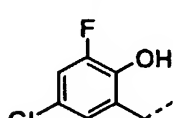
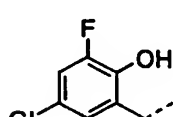
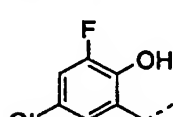
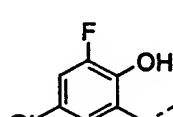
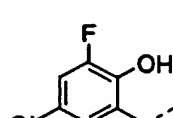
432

521		H	H	H	Me	H	H
522		H	H	H	Et	H	H
523		H	H	H	OMe	H	H
524		H	H	H	OEt	H	H
525		H	H	H	CF3	H	H
526		H	H	H	OCF3	H	H
527		H	H	H	NO2	H	H
528		H	H	H	NH2	H	H
529		H	H	H	OH	H	H
530		H	H	H	CN	H	H
531		H	H	H	COMe	H	H
532		H	H	H	COOMe	H	H

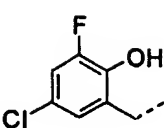
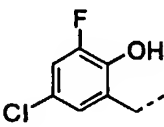
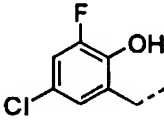
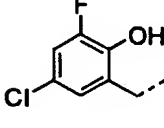
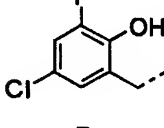
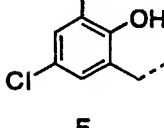
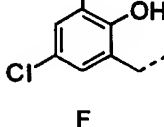
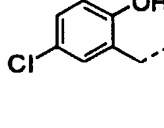
433

533		H	H	F	F	H	H
534		H	H	F	Cl	H	H
535		H	H	F	Me	H	H
536		H	H	F	Et	H	H
537		H	H	F	OMe	H	H
538		H	H	F	OEt	H	H
539		H	H	F	CF3	H	H
540		H	H	F	OCF3	H	H
541		H	H	Cl	F	H	H
542		H	H	Cl	Cl	H	H
543		H	H	Cl	Me	H	H
544		H	H	Cl	Et	H	H

434

545		H	H	Cl	OMe	H	H
546		H	H	Cl	OEt	H	H
547		H	H	Cl	CF3	H	H
548		H	H	Cl	OCF3	H	H
549		H	H	Me	F	H	H
550		H	H	Me	Cl	H	H
551		H	H	Me	Me	H	H
552		H	H	Me	Et	H	H
553		H	H	Me	OMe	H	H
554		H	H	Me	OEt	H	H
555		H	H	Me	CF3	H	H
558		H	H	Me	OCF3	H	H



557		H	H	OMe	F	H	H
558		H	H	OMe	Cl	H	H
559		H	H	OMe	Me	H	H
560		H	H	OMe	Et	H	H
561		H	H	OMe	OMe	H	H
562		H	H	OMe	OEt	H	H
563		H	H	OMe	CF3	H	H
564		H	H	OMe	OCF3	H	H

本発明は、ピペリジン化合物の薬学的に許容される酸付加体も含まれる。かかる酸として、例えば、塩酸、臭化水素酸、硫酸、リン酸、及び炭酸等の無機酸、又はマレイン酸、クエン酸、リンゴ酸、酒石酸、フマル酸、メタンスルホン酸、トリフルオロ酢酸、及び蟻酸等の有機酸が挙げられる。

さらに、本発明においては、例えばヨウ化 1 - (4 - クロロベンジル) - 1 - メチル - 4 - [ { 2 - ベンズイミダゾリル } アミノメチル ] ピペリジニウム等の、環状アミン化合物の  $C_1 \sim C_6$  アルキル付加体も含まれる。 $C_1 \sim C_6$  アルキル付加体のアルキル基としては、例えば、メチル、エチル、*n*-プロピル、*n*-ブチル、*n*-ペンチル、*n*-ヘキシル、*n*-ヘプチル、*n*-オクチル、イソプロピル、イソブチル、*sec*-ブチル、*tert*-ブチル、イソペンチル、ネオペンチル、*tert*-ペンチル、2-メチルペンチル、及び 1-エチルブチルが好適な具体例として挙げられるが、特に好ましい例としては、メチル基及びエチル基等が挙げられる。また、アンモニウム陽イオンの対陰イオンの好適な具体例としては、フッ化物、塩化物、臭化物、又はヨウ化物等のハロゲン化物陰イオンを挙げることができる。

本発明の、式 (I) で表わされる化合物は、光学活性炭素を含むことができるため、ラセミ体及び可能なすべての光学活性体も含まれる。

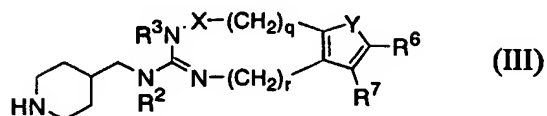
式 (I) で表される化合物の  $R^3$  が水素の場合、式 (I) で表される構造は、下記式 (II) で表される構造と区別することはできず、同一の化合物である。従って本発明は、 $R^3$  が水素の場合には、式 (I) と式 (II) の両方の構造を含む。



式（I）で表される化合物は、以下に示す一般的製造法のいずれかにより製造可能である。

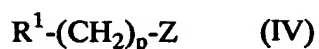
〈製造法1〉

下記式（III）



（ $R^2$ 、 $R^3$ 、 $X$ 、 $q$ 、 $r$ 、 $Y$ 、 $R^6$ 、及び $R^7$ は、式（I）においてそれぞれ定義されたものと同様である。）

で表される化合物1当量を、0.1－10当量の下記式（IV）



（ $R^1$ 及び $p$ は、式（I）においてそれぞれ定義されたものと同様である。 $Z$ はハロゲン原子、アルキルスルホニルオキシ基又はアリールスルホニルオキシ基を表す。）

で表されるアルキル化試薬で、溶媒の非存在下又は存在下で処理することによって式（I）で表される化合物を製造する。

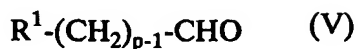
この製造法1の反応は、炭酸カリウム、炭酸カルシウム、又は炭酸水素ナトリウム等のような無機塩を含む塩基、トリエチルアミン、ジイソプロピルエチルアミン、又はピリジン等のようなアミン類、或いは（ピペリジノメチル）ポリスチレン、（モルホリノメチル）ポリスチレン、（ジエチルアミノメチル）ポリスチレン、又はポリ（4-ビニルピリジン）等のような高分子支持塩基を用いることによって、円滑に実行することができる。

この製造法1の反応は、ヨウ化カリウム又はヨウ化ナトリウム等のようなヨウ化物を添加することによって促進される場合がある。

式（III）の化合物は文献等による既知の方法で合成することが可能である。

## 〈製造法 2〉

下記式 (V)



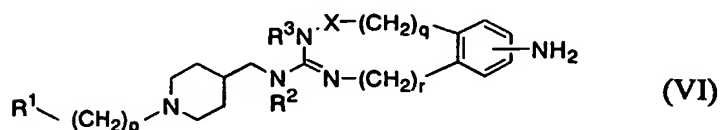
( $R^1$  及び  $p$  は、式 (I) においてそれぞれ定義されたものと同様である。)

で表されるアルデヒドの 1 当量を、式 (I I I) で表される化合物の 0.1 – 1.0 当量で、溶媒の非存在下又は存在下に処理することによって、式 (I) で表される化合物を製造する。

この製造法 2 の反応は、一般に還元的アミノ化反応と呼ばれるが、この反応条件はパラジウム、白金、ニッケル、又はロジウム等の金属を含む触媒、水素化リチウムアルミニウム、水素化ホウ素ナトリウム、水素化シアノホウ素ナトリウム、又は水素化トリアセトキシホウ素ナトリウム等の水素化物複合体、ボランによる接触水素化、或いは電解還元等によって反応させてもよい。

## 〈製造法 3〉

下記式 (V I)



( $R^1$ 、 $p$ 、 $R^2$ 、 $R^3$ 、 $X$ 、 $q$ 、及び  $r$  は、式 (I) において定義されたものと同様である。)

で表される化合物の 1 等量を、0.1 – 1.0 当量のカルボン酸又はその反応活性誘導体と溶媒の非存在下又は存在下に処理することによって、式 (I) で表される化合物を製造する。

カルボン酸の反応活性誘導体には、有機合成化学で通常使用される反応性の高いカルボン酸誘導体、例えば、酸ハロゲン化物、酸無水物、又

は混合無水物が含まれる。

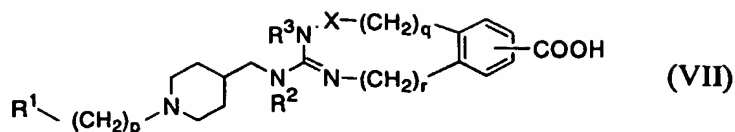
製造法 3 の反応は、適当量のモレキュラーシーブのような脱水剤、ジシクロヘキシルカルボジイミド (DCC)、N-エチル-N'-(3-ジメチルアミノプロピル)カルボジイミド (EDCI 又はWSC)、カルボジイミダゾール (CDI)、N-ヒドロキシスクシンイミド (HOSu)、N-ヒドロキシベンゾトリアゾール (HOBT)、ベンゾトリアゾール-1-イルオキシトリス (ピロリジノ)ホスホニウム、ヘキサフルオロホスフェート (PyBOP)、2-(1H-ベンゾトリアゾール-1-イル)-1,1,3,3-テトラメチルウロニウム ヘキサフルオロホスフェート (HBTU)、2-(1H-ベンゾトリアゾール-1-イル)-1,1,3,3-テトラメチルウロニウム テトラフルオロボレート (TBTU)、2-(5-ノルボルネン-2,3-ジカルボキシイミド)-1,1,3,3-テトラメチルウロニウム テトラフルオロボレート (TNTU)、O-(N-スクシンイミジル)-1,1,3,3-テトラメチルウロニウム テトラフルオロボレート (TSTU)、又はプロモトリス (ピロリジノ)ホスホニウム ヘキサフルオロホスフェート (PyBrop) 等の縮合剤を用いることによって、円滑に実行できる。

製造法 3 の反応は、製造法 1 に示す塩基を用いることによって円滑に実行できる。

式 (VI) の化合物は文献等による既知の方法で合成することが可能である。

#### <製造法 4>

下記式 (VII)



( $R^1$ 、 $p$ 、 $R^2$ 、 $R^3$ 、 $X$ 、 $q$  及び  $r$  は、式 (I) において定義されたものと同様である。)

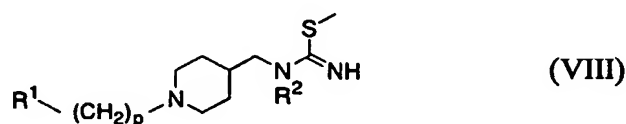
で表せる化合物の 1 等量を、0.1 – 10 当量のアミンと溶媒の非存在下又は存在下に処理することによって、式 (I) で表される化合物を製造する。

製造法 4 の反応は、製造法 3 で使用したものと同一脱水剤、縮合剤、又は塩基の適当量を用いることによって、円滑に進行させることができる。

式 (VII) の化合物は文献等による既知の方法で合成することが可能である。

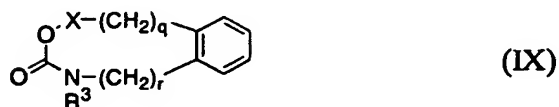
#### <製造法 5>

下記式 (VIII)



( $R^1$ 、 $R^2$ 、 $p$  は、式 (I) においてそれぞれ定義されたものと同様である。)

で表される化合物 1 当量を、0.1 – 10 当量の下記式 (IX)



( $R^3$ 、 $q$ 、 $r$  は、式 (I) においてそれぞれ定義されたものと同様で

ある。XはC Oを表す。)

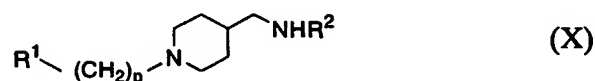
で表される酸無水物で、溶媒の非存在下または存在下で処理することによって式 (I) で表される化合物を製造する。

この製造法 5 の反応は、製造法 1 に示す塩基を用いることによって円滑に実行できる。

式 (V I I I) 及び (I X) の化合物は文献等による既知の方法で合成することが可能である。

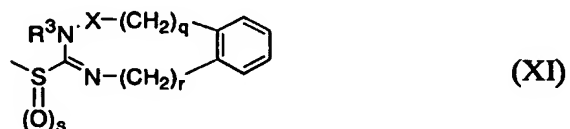
#### <製造法 6>

下記式 (X)



(R<sup>1</sup>、R<sup>2</sup>、p は、式 (I) においてそれぞれ定義されたものと同様である。)

で表される化合物 1 当量を、0.1 – 10 当量の下記式 (X I)



(R<sup>3</sup>、X、q、r は、式 (I) においてそれぞれ定義されたものと同様である。s は 0 又は 1 を表す。)

で表されるスルファニル及びスルフィニル化合物で、溶媒の非存在下又は存在下で処理することによって式 (I) で表される化合物を製造する。

この製造法 6 の反応は、製造法 1 に示す塩基や、適当な酸 (塩酸、硫酸、酢酸、安息香酸、トルエンスルホン酸、又はメタンスルホン酸等) を用いることによって円滑に実行できる。

式 (X) 及び (X I) の化合物は文献等による既知の方法で合成す

ることが可能である。

もし、製造法 1 ～ 6 のそれぞれの化合物において、各反応条件において使用される基質と反応する官能基又は有機合成化学において一般に反応に悪影響を与えると考えられる官能基を含んでいる場合には、その官能基を既知の適当な保護基で保護し、その後、各製造法の反応と、既知の工程を用いて脱保護を行い、式 (I) で表す化合物を得てもよい。

さらに本発明の化合物は、アルキル化、アシル化、又は還元等のような有機合成化学において通常使用される既知の反応を用いて、製造法 1 ～ 6 によって製造される化合物の置換基（単数又は複数）をさらに変換することによって製造してもよい。

製造法 1 ～ 6 のそれぞれにおいて、ジクロロメタン又はクロロホルム等のハロゲン化炭素、ベンゼン又はトルエン等の芳香族炭化水素、ジエチルエーテル又はテトラヒドロフラン等のエーテル類、酢酸エチル等のエステル類、ジメチルホルムアミド、ジメチルスルホキシド、又はアセトニトリル等の非プロトン性極性溶媒、メタノール、エタノール、又はイソプロピルアルコール等のアルコール類を、反応のために用いてもよい。

製造法 1 ～ 6 のいずれにおいても、反応温度は  $-78^{\circ}\text{C}$  ～  $+150^{\circ}\text{C}$  の範囲にあり、好ましくは  $0^{\circ}\text{C}$  ～  $100^{\circ}\text{C}$  である。反応完了後、濃縮、ろ過、抽出、固相抽出、再結晶、又はクロマトグラフィー等の通常の分離又は精製操作を用いて、式 (I) で表されるピペリジン誘導体を単離することができる。これらは、通常の方法によって、薬学的に許容される酸付加体又は  $\text{C}_1 - \text{C}_6$  アルキル付加体に変換することができる。

式 (I) で表わされる化合物、その薬学的に許容される酸付加体、又は、その薬学的に許容される  $\text{C}_1 - \text{C}_6$  アルキル付加体は、その治療有効量を製薬学的に許容される担体及び／又は希釈剤とともに医薬組成物



とすることによって、本発明のエオタキシン等のCCR3のリガンドが標的細胞上のCCR3に結合することを阻害する医薬、あるいはエオタキシン等のCCR3のリガンドの標的細胞への生理的作用を阻害する作用をもつ医薬、さらには、CCR3が関与すると考えられる疾患の治療薬及び／又は予防薬とすることができる。すなわち、式(I)で表わされる4, 4-二置換ピペリジン誘導体、その薬学的に許容される酸付加塩体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体は、経口的に、あるいは、静脈内、皮下、筋肉内、経皮、又は直腸内等非経口的に投与することができる。

経口投与の剤形としては、例えば錠剤、丸剤、顆粒剤、散剤、液剤、懸濁剤、カプセル剤等が挙げられる。

錠剤の形態にするには、例えば乳糖、デンプン、又は結晶セルロース等の賦形剤、カルボキシメチルセルロース、メチルセルロース、又はポリビニルピロリドン等の結合剤、及びアルギン酸ナトリウム、炭酸水素ナトリウム、又はラウリル硫酸ナトリウム等の崩壊剤等を用いて、通常の方法により成形することができる。

丸剤、散剤、又は顆粒剤も同様に上記の賦形剤等を用いて、通常の方法によって成形することができる。液剤又は懸濁剤は、例えばトリカプリリン又はトリアセチン等のグリセリンエステル類、及び／又はエタノール等のアルコール類等を用いて、通常の方法によって成形される。カプセル剤は、顆粒剤、散剤、及び／又は液剤等をゼラチン等のカプセルに充填することによって成形される。

皮下、筋肉内、又は静脈内投与の剤型としては、水性又は非水性溶液剤等の形態にある注射剤がある。水性溶液剤は、例えば生理食塩水等が用いられる。非水性溶液剤は、例えばプロピレングリコール、ポリエチレングリコール、オリーブ油、又はオレイン酸エチル等が用いられ、こ

れらに必要に応じて防腐剤及び／又は安定剤等が添加される。注射剤は、バクテリア保留フィルターを通す濾過又は殺菌剤の配合の処置等を適宜行うことによって無菌化される。

経皮投与の剤型としては、例えば軟膏剤又はクリーム剤等が挙げられ、軟膏剤は、ヒマシ油若しくはオリーブ油等の油脂類、又はワセリン等を用いて、クリーム剤は、脂肪油又はジエチレングリコール若しくはソルビタンモノ脂肪酸エステル等の乳化剤を用いて、通常の方法によって成形される。

直腸内投与のためには、ゼラチンソフトカプセル等の通常の座剤が用いられる。

本発明のピペリジン誘導体、その薬学的に許容される酸付加体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体の投与量は、疾患の種類、投与経路、患者の年齢と性別、及び疾患の程度等によって異なるが、通常成人一人当たり $1 \sim 500 \text{ mg}$ ／日である。

## 実施例

本発明を以下の実施例に基づいて具体的に説明する。しかしながら、本発明はこれら実施例によって限定されるものではない。この実施例における化合物番号は、表に好適な具体例として挙げた化合物に付けられたものを表す。実施例番号とその実施例で製造される化合物の化合物番号は同一である。

### [参考例 1-1-1]

C-[1-(3, 4-ジクロロベンジル)-ピペリジン-4-イル]  
-メチルアミンの合成

4-アミノメチル-ピペリジン(10 g)をアセトニトリル(250 ml)に溶かし、室温で3, 4-ジクロロベンジルクロリド(5.8

g) と炭酸カリウム (5 g) を加えた後、60℃で終夜攪拌した。反応溶液を濾過し、溶媒を減圧下に除去し、得られた残渣を、薄層シリカゲルクロマトグラフィー (ジクロロメタン/メタノール/トリエチルアミン=85/7/7) により精製し、C-[1-(3, 4-ジクロロベンジル)-ピペリジン-4-イル]-メチルアミンを得た。LC-MSにより同定した。

収量 6 g、収率 75%、純度 100%、実測値 ESI/MS m/e 273.2。

[参考例 1-1-2]

1-(2-アミノフェニル-3-[1-(3, 4-ジクロロベンジル)-ピペリジン-4-イルメチル]-チオウレアの合成

C-[1-(3, 4-ジクロロベンジル)-ピペリジン-4-イル]-メチルアミン (80 mg) をアセトニトリル (2 ml) に溶かし、0℃でチオカルボニルジイミダゾール (80 mg) とイミダゾール (6 mg) を加えた。室温で2時間30分攪拌後、3-ニトロ-1, 2-フェニレンジアミン (66 mg) を加え、50℃に昇温させ、12時間攪拌した。反応溶液をろ過し、溶媒を減圧下に除去し、得られた残渣を薄層シリカゲルクロマトグラフィー (ヘキサン/酢酸エチルエステル/ジクロロメタン/メタノール=60/25/10/5) により精製し、1-(2-アミノフェニル-3-[1-(3, 4-ジクロロベンジル)-ピペリジン-4-イルメチル]-チオウレアを得た。LC-MSにより同定した。

収量 75 mg、収率 61%、純度 100%、実測値 ESI/MS m/e 423.1。

[実施例 1-1-1]

(1H-ベンゾイミダゾール-2-イル)-[1-(3, 4-ジクロロ

ーベンジル)ーピペリジンー4ーイルメチル]ーアミンの合成

1ー(2ーアミノフェニルー3ー[1ー(3, 4ージクロローベンジル)ーピペリジンー4ーイルメチル]ーチオウレア(11mg、0.025mmol)にエタノール(1ml)を加えた後、酸化水銀(II)赤色(16mg、0.074mmol)と硫黄(0.3mg、0.0094mmol)を、室温で加え、7時間還流した。水銀をセライト濾過し、溶媒を減圧下に除去した。残渣をシリカゲルカラムクロマトグラフィー(ヘキサン/ジクロロメタン/メタノール/トリエチルルアミン=40/25/20/10/5)により精製し、(1Hーベンゾイミダゾールー2ーイル)ー[1ー(3, 4ージクロローベンジル)ーピペリジンー4ーイルメチル]ーアミンを得た。LCーMSにより同定した。収量8mg、収率83%、純度100%、実測値ESI/MS m/e 389.1。

[実施例1ー1ー2から実施例1ー1ー11]

化合物番号1ー1ー2から化合物番号1ー1ー11は、参考例1ー1ー1、参考例1ー1ー2、実施例1ー1ー1に従い、対応する原料より合成した。結果を表9に示す。

表9

化合物 No.1-1-	収量(mg)	収率(%)	MW	M+1
1	8	83	389.3	389.1
2	30	68	434.3	434.2
3	13	32	403.4	403.2
4	5	12	423.8	423.1
5	7	16	407.3	407.1
6	13	28	457.3	457.2
7	4	9	433.3	433.2
8	23	50	458.2	458.9
9	4	10	403.4	403.1

10	13	32	419.4	419.0
11	9	21	434.3	434.1

## [参考例 1-2-1]

4-アミノメチル-ピペリジン-1-カルボン酸 *tert*-ブチルエステルの合成

4-アミノメチルピペリジン (5.00 g、43.8 mmol) をトルエン (90 mL) に溶解し、ベンズアルデヒド (4.45 mL、43.8 mmol) を加え、Dean-Starkトラップを取り付け、2時間加熱還流した。反応液を室温まで冷却し、二炭酸-ジ-*t*-ブチル (11.5 mL、43.8 mmol) を5回に分けて加え、室温で4時間攪拌した。反応液を減圧濃縮した後に、氷浴下、硫酸水素カリウム水溶液 (1.0 M、70 mL、70 mmol) を加え、1時間激しく攪拌した。これをジエチルエーテル (30 mL × 2回) で洗浄し、水層に2規定水酸化ナトリウム水溶液を加えて、pH約7に調製した。このpH約7に調製した水溶液を酢酸エチルエステル (30 mL × 3回) で洗浄し、水層に2規定水酸化ナトリウムを加えて、pH約12に調製した。このpH約12に調製した水溶液を酢酸エチルエステル (50 mL × 4回) で抽出し、得られた有機層を無水硫酸マグネシウムで乾燥させた。これを減圧濃縮して4-アミノメチル-ピペリジン-1-カルボン酸 *tert*-ブチルエステルを得た。

収量 6.49 g、収率 70%。

## [参考例 1-2-2]

4-[(1H-ベンズイミダゾール-2-イルアミノ)-メチル]-ピペリジン-1-カルボン酸 *tert*-ブチルエステルの合成

4-アミノメチル-ピペリジン-1-カルボン酸 *tert*-ブチルエステル (3.18 g、14.8 mmol) をアセトニトリル (20 mL

）に溶解し、氷浴下でチオカルボニルジイミダゾール（3.17 g、17.8 mmol）、及びイミダゾール（302 mg、4.45 mmol）のアセトニトリル懸濁液（30 mL）を滴下した。室温まで昇温させ90分間攪拌し、これにo-フェニレンジアミン（1.93 g、17.8 mmol）を加え、50℃で2時間攪拌した。さらにジイソプロピルカルボジイミド（3.4 mL、22.2 mmol）を加え、80℃で3時間攪拌した。反応液を冷却後、減圧濃縮した後に、酢酸エチルエステル（200 mL）に溶解し、水（100 mL×2回）及び飽和食塩水（100 mL）で洗浄した。これを無水硫酸マグネシウムで乾燥させ、減圧濃縮した。濃縮残渣をシリカゲルカラムクロマトグラフィー（ジクロロメタン／メタノール＝19／1→ジクロロメタン／メタノール／トリエチルアミン＝10／1／1）で精製し、4-〔（1H-ベンズイミダゾール-2-イルアミノ）-メチル〕-ピペリジン-1-カルボン酸 tert-ブチルエステルを得た。

収量4.33 g、収率89%。

〔参考例1-2-3〕

（1H-ベンズイミダゾール-2-イル）-ピペリジン-4-イルメチル-アミンの合成

4-〔（1H-ベンズイミダゾール-2-イルアミノ）-メチル〕-ピペリジン-1-カルボン酸 tert-ブチルエステル（4.33 g、13.1 mmol）をメタノール（10 mL）に溶解し、氷浴下で4規定塩化水素-1, 4-ジオキサン溶液（33 mL、131 mmol）を少しずつ加え、室温で3時間攪拌した。反応液を氷冷し、2規定水酸化ナトリウム水溶液を加えて、pH約11とした。この水溶液に食塩を加えて飽和させ、1-ブタノール（100 mL×3回）で抽出して得られた有機層を、飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥させた。

乾燥された1-ブタノールを減圧濃縮し、(1H-ベンズイミダゾール-2-イル)-ピペリジン-4-イルメチル-アミンを得た。

収量3.0g、収率100%。

[実施例1-2-1]

(1H-ベンズイミダゾール-2-イル)-[1-(1-メチル-1H-インドール-2-イルメチル)-ピペリジン-4-イルメチル]-アミンの合成

(1H-ベンズイミダゾール-2-イル)-ピペリジン-4-イルメチル-アミン(20.0mg、0.09mmol)のジメチルホルムアミド-酢酸(10:1)溶液(1.0ml)に、1-メチル-1H-インドール-2-カルボアルデヒド(0.26mmol)とナトリウムトリアセトキシボロヒドリド(0.26mmol)を加え、室温で終夜攪拌した。反応溶液にメタノール(1.0ml)を加え、反応を停止し、1時間攪拌後、溶液をSCX(ボンドエルトSCX500MG:カチオン性イオン交換樹脂、バリアン製)に付した。メタノール、続いてクロロホルム/メタノール(1/1)混合溶液で、SCXを洗浄後、2規定アンモニアメタノール溶液で溶出した。溶媒を減圧下に留去し(1H-ベンズイミダゾール-2-イル)-[1-(1-メチル-1H-インドール-2-イルメチル)-ピペリジン-4-イルメチル]-アミンを得た。LC-MSにより同定した。

収量18mg、収率54%、純度86%、実測値ESI/MS m/e 374.2(M+1)。

[実施例1-2-2から実施例1-2-169]

化合物番号1-2-2から1-2-169の化合物は、実施例1-2-1に従い、対応する原料より合成した。結果を表10に示す。

[参考例1-2-4]

#### 4-フェニルブチルアルデヒドの合成

ニクロム酸ピリジニウム (451.5 mg, 1.20 mmol) のジクロロメタン溶液 (3.33 ml) に、モレキュラーシーブス MS4A (商品名、乾燥剤、和光純薬製) (451.5 mg) を加え、1時間攪拌した。懸濁溶液に、4-フェニルブタノール (154  $\mu$ l, 1.00 mmol) を加え、室温で1.5時間攪拌した。反応懸濁溶液をシリカゲルろ過し、濾液を減圧下に濃縮し、4-フェニルブチルアルデヒドを得た。収量 38.45 mg、収率 26%。

#### [実施例 1-2-170]

(1H-ベンズイミダゾール-2-イル) - [1-(4-フェニルブチル) - ピペリジン-4-イルメチル] - アミンの合成

(1H-ベンズイミダゾール-2-イル) - ピペリジン-4-イルメチル-アミン (30.32 mg, 0.10 mmol) と、得られた4-フェニルブチルアルデヒド (38.45 mg) のジクロロエタン (1.0 ml) とジメチルホルムアミド (0.5 ml) 混合溶液に、酢酸 (28.6  $\mu$ l) とナトリウムトリアセトキシボロヒドリド (52.99 mg, 0.25 mmol) を加え、室温で終夜攪拌した。反応懸濁溶液を SCX (ボンドエルト SCX 500 MG) に付し、SCX をクロロホルム-メタノール (1:1) 混合溶液で洗浄した。次いで、2規定アンモニアメタノール溶液で溶出し、溶媒を減圧下に留去し、残渣を得た。残渣を、HPLC 分取により精製し、(1H-ベンズイミダゾール-2-イル) - [1-(4-フェニルブチル) - ピペリジン-4-イルメチル] - アミンを得た。LC-MS により同定した。収量 19.44 mg、収率 54%、純度 89.8%、実測値 ESI/M S m/e 363.2 (M+1)。

#### [実施例 1-2-171]



化合物番号 1-2-171 の化合物は、参考例 1-2-4 に従い合成した原料アルデヒドを用いて、実施例 1-2-170 に従い合成した。結果を表 10 に示す。

[実施例 1-2-172]

(1H-ベンズイミダゾール-2-イル) - [1-(6-メトキシ-1-メチル-1H-インドール-3-イルメチル) - ピペリジン-4-イルメチル] - アミンの合成

(1H-ベンズイミダゾール-2-イル) - ピペリジン-4-イルメチル-アミン (20 mg、0.09 mmol)、(6-メトキシ-1-メチル-1H-インドール-3-イルメチル) - トリメチルアンモニウムヨウ化物 (0.1 mmol)、及び無水炭酸カリウム (5 mg、0.11 mmol) に、無水アセトニトリル (2 ml) を加え、50℃で 12 時間攪拌した。室温に冷却し、シリカゲルショートカラムに付した後、分取 HPLC により精製し、(1H-ベンズイミダゾール-2-イル) - [1-(6-メトキシ-1-メチル-1H-インドール-3-イルメチル) - ピペリジン-4-イルメチル] - アミンを得た。LC-MS により同定した。

収量 5.66 mg、収率 13%、純度 96.3%、実測値 ESI/MS m/e 404.4 (M+1)。

[実施例 1-2-173 から実施例 1-2-180]

化合物番号 1-2-173 から化合物番号 1-2-180 までの化合物は、実施例 1-2-172 に従い、対応する各種ハロゲン化物、又は 4 級アンモニウムハロゲン化物より合成した。結果を表 10 に示す。

表 10

化合物 No.1-2-	収量(mg)	収率(%)	MW	M+1
1	18	54	373.5	374.2

2	29	54	370.5	371.2
3	11	41	320.4	321.2
4	23	76	354.9	355.2
5	9	29	334.5	335.2
6	28	82	388.4	389.2
7	23	74	362.5	363.2
8	21	71	345.4	346.2
9	33	96	398.5	399.2
10	16	48	378.5	379.2
11	21	68	350.5	351.2
12	16	82	326.5	327.2
13	8	40	334.5	335.2
14	19	91	348.5	349.3
15	25	78	359.5	360.2
16	18	54	373.5	374.2
17	12	42	310.4	311.2
18	21	70	326.5	327.1
19	22	62	390.6	391.2
20	14	48	321.4	322.2
21	15	53	321.4	322.2
22	15	46	371.5	372.2
23	14	41	371.5	372.2
24	17	57	327.5	328.1
25	21	75	310.4	311.2
26	22	79	310.4	311.2
27	24	65	414.6	415.2
28	6	17	413.6	414.2
29	23	69	374.5	375.2
30	20	70	334.5	335.6
31	15	50	345.4	346.5
32	22	63	396.5	397.2
33	21	68	350.5	351.2
34	18	58	354.9	355.3

35	15	43	389.3	389.4
36	21	68	354.9	355.3
37	16	51	365.4	366.3
38	15	45	388.4	389.4
39	15	43	399.3	399.1
40	16	54	334.5	335.4
41	15	53	336.4	337.2
42	22	74	336.4	337.2
43	13	41	363.5	364.2
44	18	54	377.5	378.2
45	21	68	364.5	365.2
46	11	33	378.5	379.2
47	15	46	378.5	379.2
48	17	45	426.6	427.2
49	23	63	426.6	427.2
50	22	69	370.5	371.4
51	21	66	364.5	365.3
52	18	57	360.5	361.2
53	21	57	420.9	421.5
54	21	55	396.5	397.4
55	7	20	388.5	389.3
56	10	41	403.5	404.2
57	3	13	387.5	388.2
58	22	100	338.4	339.2
59	22	67	321.4	322.2
60	19	56	338.4	339.1
61	24	68	350.5	351.2
62	23	100	378.5	379.2
63	30	100	412.5	413.2
64	17	70	404.4	405.1
65	28	100	389.3	389.1
66	14	57	406.4	407.1
67	30	83	364.4	365.1

68	20	43	456.4	457.1
69	28	78	352.4	353.2
70	29	69	412.5	413.2
71	33	78	426.6	427.2
72	34	86	399.3	400.1
73	28	82	345.4	346.2
74	24	54	442.6	443.2
75	25	68	365.4	366.2
76	35	81	426.6	427.2
77	26	57	447.0	447.2
78	28	72	380.5	381.2
79	22	58	380.5	381.2
80	17	78	362.5	363.2
81	20	90	370.9	371.1
82	20	90	372.9	373.1
83	19	69	456.6	457.2
84	8	32	417.3	417.1
85	12	47	429.4	429.2
86	17	69	408.5	409.3
87	18	79	381.4	382.2
88	20	87	381.4	382.2
89	11	46	399.9	400.1
90	20	88	378.5	379.2
91	16	73	364.4	365.2
92	15	58	430.5	431.3
93	16	67	400.5	401.3
94	20	81	413.6	414.3
95	12	50	400.5	401.3
96	13	52	414.6	415.3
97	19	78	408.5	409.3
98	22	62	350.5	351.5
99	10	27	380.4	381.2
100	29	80	366.5	367.1

101	3	6	456.6	457.3
102	13	37	352.4	353.2
103	15	40	366.5	367.2
104	15	56	449.4	450.2
105	15	61	410.5	411.3
106	16	69	389.3	389.2
107	11	51	356.4	357.2
108	10	39	422.9	423.2
109	10	41	406.4	407.2
110	2	8	392.5	393.7
111	4	15	395.5	396.3
112	6	27	359.5	360.3
113	16	47	376.5	377.3
114	19	50	420.6	421.4
115	4	11	420.6	421.4
116	14	40	401.5	402.4
117	17	54	370.9	371.2
118	14	39	415.3	417.1 (Br)
119	8	25	381.4	382.2
120	7	21	383.4	384.2
121	10	32	354.4	355.2
122	6	17	392.5	393.3
123	18	56	368.5	369.2
124	22	61	417.3	419.1 (Br)
125	26	69	429.4	429.2
126	21	67	366.5	367.3
127	27	85	443.4	445.2 (Br)
128	23	66	399.9	400.2
129	31	91	394.5	395.3
130	20	61	370.4	371.2
131	30	91	372.9	373.2
132	22	60	422.6	423.2
133	22	70	364.5	365.2

134	22	72	352.5	353.2
135	19	57	399.9	400.1
136	24	74	378.5	379.2
137	3	91	420.4	421.3
138	11	35	348.5	349.3
139	10	28	424.5	425.3
140	8	25	380.5	381.2
141	20	51	455.6	456.3
142	13	37	404.6	405.3
143	13	38	389.3	389.1
144	17	43	450.5	451.3
145	20	58	400.5	401.3
146	24	63	437.6	438.3
147	21	61	390.6	391.2
148	5	17	336.4	337.1
149	11	33	364.4	365.1
150	7	19	405.3	405.1
151	2	6	386.5	387.1
152	5	14	386.5	387.1
153	1	4	428.5	429.2
154	8	8	369.9	370.1
155	6	20	365.4	366.1
156	5	16	365.4	366.1
157	6	20	338.4	366.1
158	10	12	335.5	336.1
159	11	29	420.5	421.1
160	9	23	462.3	463.1
161	17	53	364.4	365.1
162	10	26	449.8	451.0 (Br)
163	23	23	371.5	372.1
164	17	17	386.4	387.1
165	7	20	384.9	385.1
166	5	10	588.2	589.0

167	14	38	438.9	439.2
168	9	23	438.9	439.1
169	15	46	370.9	371.1
170	19	54	362.5	363.2
171	31	82	376.5	377.3
172	6	13	403.5	404.4
173	3	8	387.5	388.3
174	6	18	387.5	388.2
175	23	70	384.5	385.2
176	9	27	384.5	385.2
177	8	22	401.6	402.3
178	5	13	387.5	388.2
179	7	20	387.5	388.4
180	2	5	449.6	450.5

## [参考例 1 - 3 - 1]

4 - [ ( 4 - ニトロ - 1 H - ベンズイミダゾール - 2 - イルアミノ ) - メチル ] - ピペリジン - 1 - カルボン酸 *tert* - ブチルエステルの合成

4 - アミノメチル - ピペリジン - 1 - カルボン酸 *tert* - ブチルエステル ( 2 g ) をアセトニトリル ( 1 0 0 m l ) に溶かし、0℃で、チオカルボニルジイミダゾール ( 2 g ) とイミダゾール ( 0 . 2 g ) を加えた。室温で2時間30分攪拌後、3 - ニトロ - 1 , 2 - フェニレンジアミン ( 2 . 1 g ) を加え、50℃に昇温し、12時間攪拌した。ジイソプロピルカルボジイミド ( 2 . 4 g ) を加え、3時間30分還流させた後、溶媒を減圧下に除去し、得られた残渣をシリカゲルクロマトグラフィー ( ジクロロメタン / ヘキサン = 7 / 3 → 1 / 0 ) により精製し、4 - [ ( 4 - ニトロ - 1 H - ベンズイミダゾール - 2 - イルアミノ ) - メチル ] - ピペリジン - 1 - カルボン酸 *tert* - ブチルエステル得た

。LC-MSにより同定した。

収量 3.5 g、収率 100%、純度 95%、実測値ESI/MS m/e 376.4 (M+1)。

[参考例 1-3-2]

(4-ニトロ-1H-ベンズイミダゾール-2-イル)-ピペリジン-4-イルメチル-アミンの合成

4-[(4-ニトロ-1H-ベンズイミダゾール-2-イルアミノ)-メチル]-ピペリジン-1-カルボン酸 tert-ブチルエステル (13 mg) をメタノール (1 ml) に溶かし、4 規定塩化水素-1, 4-ジオキサン溶液 (1 ml) を加え、60℃で1時間攪拌した。溶媒を減圧下に留去し、得られた残渣に水酸化ナトリウム水溶液とジクロロメタンを加え、ジクロロメタンで抽出を行った。溶媒を減圧下に留去し、(4-ニトロ-1H-ベンズイミダゾール-2-イル)-ピペリジン-4-イルメチル-アミンを得た。LC-MSにより同定した。収量 8 mg、収率 83%、純度 100%、実測値ESI/MS m/e 276.1 (M+1)。

[参考例 1-3-3]

(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)- (4-ニトロ-1H-ベンズイミダゾール-2-イル)-アミンの合成

(4-ニトロ-1H-ベンズイミダゾール-2-イル)-ピペリジン-4-イルメチル-アミン (450 mg、1 mmol) のジメチルホルムアミド-酢酸 (10:1) 溶液 (7 mL) に、1-ナフトアルデヒド (3 mmol) とナトリウムトリアセトキシボロヒドリド (3 mmol) を加え、室温で終夜攪拌した。水とジクロロメタンを加え、ジクロロメタンで抽出を行った。溶媒を減圧下に留去した後、シリカゲルカラムクロマトグラフィー (酢酸エチルエステル/トリエチルルアミン=10



0/0→98/2)により精製し、(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-(4-ニトロ-1H-ベンズイミダゾール-2-イル)-アミンを得た。LC-MSにより同定した。

収量500mg、収率100%、純度100%、実測値ESI/MS m/e 394.0 (M+1)。

[参考例1-3-4]

4-アミノ-2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-ベンズイミダゾール-1-カルボン酸 tert-ブチルエステルの合成

(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-(4-ニトロ-1H-ベンズイミダゾール-2-イル)-アミン(500mg)を、1,4-ジオキサン(15ml)に溶かし、二炭酸ジ-tert-ブチル(1g)を加え、50℃で2時間攪拌した。溶媒を減圧下に除去し、得られた残渣をヘキサン(5ml×5回)で洗浄した。残渣をテトラヒドロフラン(10ml)に溶かし、ラネーニッケル(500mg)を加え、水素気流下室温で終夜攪拌した。反応液をセライト濾過した後、溶媒を減圧下に留去し、4-アミノ-2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-ベンズイミダゾール-1-カルボン酸 tert-ブチルエステルを得た。LC-MSにより同定した。

収量200mg、収率39%、純度100%、実測値ESI/MS m/e 464.3 (M+1)。

[実施例1-3-1]

3-アセチルアミノ-N-{2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-4-イル}-プロピオンアミドの合成

4-アミノ-2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-ベンズイミダゾール-1-カルボン酸 *tert*-ブチルエステル (0.02 mmol) をテトラヒドロフラン (1 ml) に溶かし、ジイソプロピルカルボジイミド (0.05 mmol) と1-ヒドロキシベンゾトリアゾール-水和物 (0.05 mmol) と3-アセチルアミノプロピオン酸 (0.05 mmol) を加え、室温で終夜攪拌した。反応液に、4規定塩化水素-1, 4-ジオキサン溶液 (1 ml) を加え、50℃で1時間攪拌後、溶媒を減圧下に除去し、得られた残渣にジクロロメタンと5規定水酸化ナトリウム水溶液を加え攪拌した。有機層をSCX (ボンドエルトSCX500MG) に付し、メタノールでSCXを洗浄後、2規定アンモニアメタノール溶液で溶出した。溶媒を減圧下に留去し、3-アセチルアミノ-N-{2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-4-イル}-プロピオンアミドを得た。LC-MSにより同定した。

収量0.4 mg、収率4%、純度100%、実測値ESI/MS  $m/e$  499.3 (M+1)。

[実施例1-3-2から実施例1-3-8]

化合物番号1-3-2から1-3-8の化合物は、参考例1-3-1から参考例1-3-4、及び実施例1-3-1に従い、対応する原料より合成した。結果を表11に示す。

[実施例1-3-9]

N-(2-{[1-(3, 4-ジクロロベンジル)-ピペリジン-4-イルメチル]-アミノ}-1H-ベンズイミダゾール-4-イル)-ブチルアミドの合成

4-アミノ-2-{[1-(3, 4-ジクロロベンジル)-ピペリジ

ン-4-イルメチル]-アミノ}-ベンズイミダゾール-1-カルボン酸 *tert*-ブチルエステル (10 mg, 0.02 mmol) を、テトラヒドロフラン (1 ml) に溶かし、トリエチルアミン (5.6  $\mu$ l, 0.04 mmol) とブチリルクロリド (8.3  $\mu$ l, 0.08 mmol) を加え、室温で1時間30分攪拌した。反応液に4規定塩化水素-1, 4-ジオキサン溶液 (1 ml) を加え、50℃で2時間攪拌した。溶媒を減圧下に除去し、得られた残渣にジクロロメタンと5規定水酸化ナトリウム水溶液を加え、攪拌後、有機層をSCX (ボンドエルト SCX 500 MG) に付した。メタノールでSCXを洗浄後、2規定アンモニアメタノール溶液で溶出した。溶媒を減圧下に留去し、N-(2-{[1-(3, 4-ジクロロベンジル)-ピペリジン-4-イルメチル]-アミノ}-1H-ベンズイミダゾール-4-イル)-ブチルアミドを得た。LC-MSにより同定した。

収量 4.9 mg、収率 52%、純度 100%、実測値 ESI/MS  $m/e$  474.0 (M+1)。

なお、原料である4-アミノ-2-{[1-(3, 4-ジクロロベンジル)-ピペリジン-4-イルメチル]-アミノ}-ベンズイミダゾール-1-カルボン酸 *tert*-ブチルエステルは、参考例1-3-1から参考例1-3-4に従い、対応する原料より合成した。

[実施例1-3-10から実施例1-3-56]

化合物番号1-3-10から1-3-56の化合物は、実施例1-3-9に従い、対応する原料より合成した。結果を表11に示す。

[実施例1-3-57]

プロパン-1-スルホン酸 (2-{[1-(3, 4-ジクロロベンジル)-ピペリジン-4-イルメチル]-アミノ}-1H-ベンズイミダゾール-4-イル)-アミドの合成

4-アミノ-2- { [1- (3, 4-ジクロロ-ベンジル) -ピペリジン-4-イルメチル] -アミノ} -ベンズイミダゾール-1-カルボン酸 *tert*-ブチルエステル (10 mg、0.02 mmol) を、テトラヒドロフラン (1 ml) に溶かし、トリエチルアミン (0.04 mmol) とプロパン-1-スルホンクロリド (0.08 mmol) を加え、室温で終夜攪拌した。反応液に4規定塩化水素-1, 4-ジオキサン溶液 (1 ml) を加え、50℃で1時間攪拌した。溶媒を減圧下に除去し、得られた残渣にジクロロメタンと5規定水酸化ナトリウム水溶液を加え、攪拌後、有機層をSCX (ボンドエルトSCX500MG) に付した。メタノールでSCXを洗浄後、2規定アンモニアメタノール溶液で溶出した。溶媒を減圧下に留去し、プロパン-1-スルホン酸 (2- { [1- (3, 4-ジクロロ-ベンジル) -ピペリジン-4-イルメチル] -アミノ} -1H-ベンズイミダゾール-4-イル) -アミドを得た。LC-MSにより同定した。

収量0.8 mg、収率8%、純度100%、実測値ESI/MS m/e 510.1 (M+1)。

#### [実施例1-3-58]

化合物番号1-3-58の化合物は、実施例1-3-57に従い、対応する原料より合成した。結果を表11に示す。

#### [実施例1-3-59]

1- (2- { [1- (3, 4-ジクロロ-ベンジル) -ピペリジン-4-イルメチル] -アミノ} -1H-ベンズイミダゾール-4-イル) -3-エチル-ウレアの合成

4-アミノ-2- { [1- (3, 4-ジクロロ-ベンジル) -ピペリジン-4-イルメチル] -アミノ} -ベンズイミダゾール-1-カルボン酸 *tert*-ブチルエステル (10 mg、0.02 mmol) をアセト

ニトリル（1 ml）に溶かし、エチルイソシアナート（0.08 mmol）を加え、室温で終夜攪拌した。反応液に、4規定塩化水素－1，4－ジオキサン溶液（1 ml）を加え、50℃で1時間攪拌後、反応液をSCX（ボンドエルトSCX500MG）に付した。メタノールでSCXを洗浄後、2規定アンモニアメタノール溶液で溶出した。溶媒を減圧下に留去し、1－（2－{[1－（3，4－ジクロロベンジル）－ピペリジン－4－イルメチル]－アミノ}－1H－ベンズイミダゾール－4－イル）－3－エチル－ウレアを得た。LC－MSにより同定した。

収量1.6 mg、収率17%、純度96%、実測値ESI/MS m/e 475.1（M+1）。

〔実施例1－3－60〕

化合物番号1－3－60の化合物は、実施例1－3－59に従い、対応する原料より合成した。結果を表11に示す。

〔実施例1－3－61〕

N2－[1－（3，4－ジクロロベンジル）－ピペリジン－4－イルメチル]－1H－ベンズイミダゾール－2，4－ジアミンの合成

4－アミノ－2－{[1－（3，4－ジクロロベンジル）－ピペリジン－4－イルメチル]－アミノ}－ベンズイミダゾール1－カルボン酸tert－ブチルエステル（10 mg、0.02 mmol）を、メタノール（1 ml）に溶かし、4規定塩化水素－1，4－ジオキサン溶液（1 ml）を加え、50℃で1時間攪拌した。反応液をSCX（ボンドエルトSCX500MG）に付し、メタノールでSCXを洗浄後、2規定アンモニアメタノール溶液で溶出した。溶媒を減圧下に留去し、N2－[1－（3，4－ジクロロベンジル）－ピペリジン－4－イルメチル]－1H－ベンズイミダゾール－2，4－ジアミンを得た。LC－M

Sにより同定した。

収量 6.5 mg、収率 80%、純度 100%、実測値 ESI/MS m/e 404.1 (M+1)。

[実施例 1-3-62]

化合物番号 1-3-62 の化合物は、実施例 1-3-61 に従い、対応する原料より合成した。結果を表 11 に示す。

表 11

化合物 No.1-3-	収量(mg)	収率(%)	MW	M+1
1	0.4	4	498.6	499.3
2	2	24	490.4	489.9
3	4	39	462.6	463.3
4	5	50	476.6	477.1
5	1	12	484.6	485.4
6	2	23	499.0	499.1
7	3	29	490.4	490.1
8	3	30	475.4	475.1
9	5	52	474.4	474.0
10	4	16	488.5	488.4
11	4	12	565.5	565.4
12	4	14	557.5	557.5
13	24	92	520.5	520.4
14	1	3	551.5	551.5
15	39	100	514.5	514.4
16	2	8	499.4	499.4
17	28	100	509.4	509.5
18	30	100	506.5	506.4
19	3	11	488.5	488.4
20	1	4	546.5	546.4
21	30	100	509.4	509.5
22	31	100	509.4	509.5
23	29	100	552.5	552.4

24	1	4	553.4	553.4
25	14	53	528.5	528.4
26	17	67	514.5	514.4
27	2	8	498.4	498.4
28	19	73	514.5	514.4
29	15	57	528.5	528.4
30	17	68	500.5	500.5
31	4	15	486.4	486.4
32	21	89	472.4	472.4
33	20	86	460.4	460.4
34	40	100	458.4	458.4
35	16	66	476.4	476.3
36	19	69	552.5	538.4
37	19	80	474.4	474.2
38	19	76	488.5	488.3
39	19	71	522.5	522.5
40	1	4	538.5	538.4
41	3	11	542.9	542.4
42	17	65	508.5	508.4
43	5	22	446.4	446.1
44	7	68	518.4	518.0
45	8	76	522.5	522.0
46	9	88	536.5	536.3
47	2	6	504.4	504.0
48	2	7	503.4	503.3
49	3	10	476.4	476.0
50	2	6	475.4	475.2
51	5	19	517.5	517.1
52	6	67	446.4	446.1
53	6	55	536.5	536.3
54	5	47	474.4	474.0
55	2	23	522.5	522.0
56	1	10	504.4	503.9

57	1	8	510.5	510.1
58	4	37	510.5	510.2
59	2	17	475.4	475.1
60	2	17	475.4	475.0
61	7	80	404.3	404.1
62	9	72	404.3	404.1

## [参考例 1-4-1]

## 3-ニトロフタル酸の合成

4-ニトロイソベンゾフラン-1, 3-ジオン (20.0 g、0.104 mol) を、50℃に加温したアンモニア水溶液 (28%、28 ml) に少しずつ加えた。30分間攪拌した後に、反応液を氷冷して、析出物を濾取、乾燥することによりアンモニウム塩を得た。この塩を水 (40 ml) に懸濁し、濃塩酸を滴下して、pH 約 2 に調製した。沈殿した固体を濾取、乾燥して、3-ニトロフタル酸を得た。NMR により同定した。

収量 12.3 g、収率 56%。

$^1\text{H-NMR}$  (270 MHz,  $\text{CD}_3\text{OD}$ ) :  $\delta$  8.28 (1H, dd,  $J = 7.6, 1.2$  Hz), 8.25 (1H, dd,  $J = 7.8, 1.2$  Hz), 7.72 (1H, dd,  $J = 7.8, 7.6$  Hz) ppm

## [参考例 1-4-2]

## 2-アミノ-3-ニトロ安息香酸の合成

水酸化カリウム (4.27 g、76.2 mmol) を水 (22 ml) に溶解し、氷冷しながら、臭素 (0.463 ml、9.50 mmol) を滴下した。これに 3-ニトロフタル酸 (2.00 g、9.52 mmol) を加え、すべて溶解した後に、60℃で3時間攪拌し、さらに室



温で終夜攪拌を続けた。反応液を氷冷し、橙色の析出物を濾取した。これを水20mlに溶解し、濃塩酸を滴下して、pH4に調製した。氷冷後、黄色の析出物を濾取して乾燥し、2-アミノ-3-ニトロ-安息香酸を得た。NMRにより同定した。

収量1.03g、収率59%。

$^1\text{H-NMR}$  (270MHz,  $\text{CD}_3\text{OD}$ ) :  $\delta$  8.33 (1H, dd,  $J=8.4, 1.7\text{ Hz}$ ), 8.27 (1H, dd,  $J=7.6, 1.7\text{ Hz}$ ), 6.67 (1H, dd,  $J=8.7, 7.6\text{ Hz}$ ) ppm.

[参考例1-4-3]

2-アミノ-3-ニトロ-安息香酸メチルエステルの合成

2-アミノ-3-ニトロ-安息香酸 (1.00g、5.49mmol) をメタノール (40ml) に溶解し、硫酸 (0.50ml) を加えて、2日間加熱還流した。反応液を室温に冷却後、飽和炭酸水素ナトリウム水溶液で、pH約9に調製して、約10mlに減圧濃縮した。水 (20ml) を加えてから、酢酸エチルエステル (10ml×3回) で抽出し、得られた有機層を無水硫酸マグネシウムで乾燥させた。これを減圧濃縮して生じた結晶を乾燥し、2-アミノ-3-ニトロ-安息香酸メチルエステルを得た。NMRにより同定した。

収量661.4mg、収率61%。

$^1\text{H-NMR}$  (270MHz,  $\text{CDCl}_3$ ) :  $\delta$  8.50 (br), 8.37 (1H, dd,  $J=8.6, 1.4\text{ Hz}$ ), 8.23 (1H, dd,  $J=7.6, 1.4\text{ Hz}$ ), 6.65 (1H, dd,  $J=8.6, 7.6\text{ Hz}$ ), 3.92 (3H, s) ppm.

[参考例1-4-4]

2,3-ジアミノ-安息香酸メチルエステルの合成

2-アミノ-3-ニトロ-安息香酸メチルエステル (661mg、3.37mmol) をメタノール (30ml) に溶解し、窒素気流下で、10%パラジウム-カーボン粉末 (5mol%) を加え、水素雰囲気下で1時間攪拌した。反応液をセライトを通じて濾過し、得られた濾液を減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー (n-ヘキサン/酢酸エチルエステル=2/1) で精製して、2,3-ジアミノ-安息香酸メチルエステルを得た。NMRにより同定した。

収率517.2mg、収量92%。

$^1\text{H-NMR}$  (270MHz,  $\text{CDCl}_3$ ) :  $\delta$  7.46 (1H, dd,  $J=8.2\text{Hz}$ ,  $1.5\text{Hz}$ ), 6.85 (1H, dd,  $J=8.2\text{Hz}$ ,  $1.5\text{Hz}$ ), 6.60 (1H, t,  $J=8.2\text{Hz}$ ), 5.53 (br), 3.87 (3H, s), 3.35 (br) ppm.

[参考例1-4-5]

2-[(1-tert-ブトキシカルボニル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-4-カルボン酸メチルエステルの合成

4-アミノメチル-ピペリジン-1-カルボン酸 tert-ブチルエステル (3.29g、15.4mmol) をアセトニトリル (40ml) に溶解し、氷浴で冷却した。これに1,1-チオカルボニルジイミダゾール (3.28g、18.4mmol) 及びイミダゾール (314mg、4.6mmol) のアセトニトリル溶液 (30ml) を滴下し、室温まで昇温しながら2時間攪拌した。反応液に2,3-ジアミノ-安息香酸メチルエステル (3.07g、18.5mmol) を加え、50℃で終夜攪拌した。その後に、ジイソプロピルカルボジイミド (2.84ml、18.5mmol) を加えて80℃で2時間攪拌した。反応液を減圧濃縮して得られた残渣を、シリカゲルカラムクロマトグラフィー (

n-ヘキサン／酢酸エチルエステル＝3／2→酢酸エチルエステル／メタノール／トリエチルアミン＝10／1／0.1)で精製して、2-[(1-tert-ブトキシカルボニル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-4-カルボン酸メチルエステルを得た。LC-MSにより同定した。

収量5.47 g、収率91.4%、 $[M+1] = 389.2$ 。

[参考例1-4-6]

2-[(ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-4-カルボン酸メチルエステルの合成

2-[(1-tert-ブトキシカルボニル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-4-カルボン酸メチルエステル(2.28 g、5.87 mmol)をメタノール(3 ml)に溶解し、4規定塩化水素-1,4-ジオキサン溶液(10 ml、40 mmol)を加え、室温で終夜攪拌した。析出した結晶を濾取し、酢酸エチルエステルで洗浄後に乾燥して、2-[(ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-4-カルボン酸メチルエステルを得た。LC-MSにより同定した。

収量1.19 g、収率56.1%、 $[M+1] = 289.2$ 。

[実施例1-4-1]

2-{[1-(3,5-ジクロロ-2-ヒドロキシ-ベンジル)-ピペリジン-4-イルメチル]-アミノ}-1H-ベンズイミダゾール-4-カルボン酸メチルエステルの合成

2-[(ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-4-カルボン酸メチルエステル(20 mg、0.055 mmol)をジメチルスルホキシド-酢酸(10:1)に溶解し、2-ヒドロキシ-3,5-ジクロロベンズアルデヒド(32.0 mg、0.1

66 mmol) 及びナトリウムトリアセトキシボロヒドリド (35.0 mg、0.166 mmol) を加え、50℃で2日間攪拌した。反応液にメタノール (1 ml) を加えて、1分間攪拌した後に、SCX固相抽出 (ボンドエルト SCX 500 MG) にて精製した。これをさらに分取 HPLC で精製して、2- { [1- (3, 5-ジクロロ-2-ヒドロキシベンジル) -ピペリジン-4-イルメチル] -アミノ } -1H-ベンズイミダゾール-4-カルボン酸メチルエステルを得た。LC-MS により同定した。

収量 10.1 mg、収率 39.3%、純度 94.0%、 $[M+1] = 463.1$

[実施例 1-4-2 から実施例 1-4-9]

化合物番号 1-4-2 から 1-4-9 までの化合物は、実施例 1-4-1 に従い、対応する原料より合成した。結果を表 12 に示す。

[参考例 1-4-7]

2- [ (1-tert-ブトキシカルボニル-ピペリジン-4-イルメチル) -アミノ ] -1H-ベンズイミダゾール-4-カルボン酸の合成

2- [ (1-tert-ブトキシカルボニル-ピペリジン-4-イルメチル) -アミノ ] -1H-ベンズイミダゾール-4-カルボン酸メチルエステル (5.47 g、14.1 mmol) をメタノール (60 ml) に溶解し、水酸化リチウム水溶液 (4 mmol/L、20 ml、80 mmol) を加え、50℃で終夜攪拌した。反応液を氷浴で冷却し、6規定塩酸 (5 ml) を滴下した。さらに1規定塩酸を徐々に加えながら、pH 約 7.5 に調製し、氷浴中1時間攪拌を続けた。析出物を濾取して、酢酸エチルエステル及び水で洗浄した。これを減圧乾燥して 2- [ (1-tert-ブトキシカルボニル-ピペリジン-4-イルメチル) -アミノ ] -1H-ベンズイミダゾール-4-カルボン酸を得た。LC-

MSにより同定した。

収量 3.68 g、収率 69.7%、 $[M+1] = 375.2$ 。

[参考例 1-4-8]

4- { [4- (2-メトキシエチルカルバモイル) -1H-ベンズイミダゾール-2-イルアミノ] -メチル} -ピペリジン-1-カルボン酸 tert-ブチルエステルの合成

2- [ (1-tert-ブトキシカルボニル-ピペリジン-4-イルメチル) -アミノ] -1H-ベンズイミダゾール-4-カルボン酸 (1.20 g、3.20 mmol) を、ジメチルホルムアミドとテトラヒドロフランの混合溶媒 (1:1, 20 ml) に懸濁させ、1-ヒドロキシベンゾトリアゾール-水和物 (737 mg、4.81 mmol) 及び 2-メトキシエチルアミン (0.42 ml、4.8 mmol) を加えた。さらに 1-エチル-3- (3-ジメチルアミノプロピル) カルボジイミド塩酸塩 (1.90 g、6.40 mmol) を加えた後、室温で 4 時間攪拌した。反応液に水 (100 ml) を加え、酢酸エチルエステル (150 ml × 3 回) で抽出し、有機層を飽和食塩水 (100 ml) で洗浄後、無水硫酸マグネシウムで乾燥させた。これを減圧濃縮して得られた残渣を、シリカゲルカラムクロマトグラフィー (酢酸エチルエステル/メタノール = 30/1) で精製して、4- { [4- (2-メトキシエチルカルバモイル) -1H-ベンズイミダゾール-2-イルアミノ] -メチル} -ピペリジン-1-カルボン酸 tert-ブチルエステルを得た。LC-MS により同定した。

収量 1.30 g、収率 94.1%、純度:  $[M+1] = 432.2$ 。

[参考例 1-4-9]

2- [ (ピペリジン-4-イルメチル) -アミノ] -1H-ベンズイミダゾール-4-カルボン酸 (2-メトキシエチル) -アミドの合成

4- { [ 4- ( 2-メトキシ-エチルカルバモイル) - 1 H-ベンズイミダゾール- 2-イルアミノ] -メチル} -ピペリジン- 1-カルボン酸 *tert*-ブチルエステル ( 1. 3 0 g、 3. 0 1 mmol ) をメタノール ( 1 ml ) に溶解し、 4 規定塩化水素- 1, 4-ジオキサン溶液 ( 7. 0 ml、 2 8. 0 mmol ) を加え、 5 0℃で 1 時間攪拌した。反応液を減圧濃縮、真空乾燥して、 2- [ (ピペリジン- 4-イルメチル) -アミノ] - 1 H-ベンズイミダゾール- 4-カルボン酸 ( 2-メトキシ-エチル) -アミドを得た。LC-MSにより同定した。

収量 1. 2 3 g、収率 1 0 0 %、純度： [ M + 1 ] = 3 3 2. 2。

[実施例 1-4-10]

2- { [ 1- ( 5-クロロ- 2-ヒドロキシ-ベンジル) -ピペリジン- 4-イルメチル] -アミノ} - 1 H-ベンズイミダゾール- 4-カルボン酸 ( 2-メトキシ-エチル) -アミドの合成

2- [ (ピペリジン- 4-イルメチル) -アミノ] - 1 H-ベンズイミダゾール- 4-カルボン酸 ( 2-メトキシ-エチル) -アミド ( 2 0 mg、 0. 0 4 9 mmol ) を、ジメチルスルホキシド-酢酸 ( 1 0 : 1、 0. 5 0 ml ) に溶解し、 2-ヒドロキシ- 5-クロロベンズアルデヒド ( 2 3 mg、 0. 1 5 mmol )、及びナトリウムトリアセトキシボロヒドリド ( 3 1 mg、 0. 1 5 mg ) を加え、 5 0℃で 2 日間攪拌した。反応液にメタノール ( 1 ml ) を加えて、 1 分間攪拌した後、SCX固相抽出 (ボンドエルト SCX 5 0 0 MG) にて精製した。これをさらに分取 HPLC で精製して、 2- { [ 1- ( 5-クロロ- 2-ヒドロキシ-ベンジル) -ピペリジン- 4-イルメチル] -アミノ} - 1 H-ベンズイミダゾール- 4-カルボン酸 ( 2-メトキシ-エチル) -アミドを得た。LC-MSにより同定した。

収量 9. 4 mg、収率 4 0. 6 %、純度 9 4. 0 %、 [ M + 1 ] = 4 7

2. 2.

[実施例 1-4-11 から実施例 1-4-17]

化合物番号 1-4-11 から 1-4-17 の化合物の合成は、実施例 1-4-10 に従い、対応する原料より合成した。結果を表 12 に示す。

[参考例 1-4-9]

2- { [1- (3, 5-ジクロロ-2-ヒドロキシ-ベンジル) -ピペリジン-4-イルメチル] -アミノ} -1H-ベンズイミダゾール-4-カルボン酸の合成

2- { [1- (3, 5-ジクロロ-2-ヒドロキシ-ベンジル) -ピペリジン-4-イルメチル] -アミノ} -1H-ベンズイミダゾール-4-カルボン酸メチルエステル (993 mg、2.14 mmol) をメタノール (10 ml) に懸濁し、水酸化リチウム水溶液 (4 M、5.4 ml、21.4 mmol) を加えた。反応液を 50℃ で 2 時間攪拌した後に、室温に冷却した。これに 1 規定塩酸を滴下して、pH 約 6.0 に調製した。酢酸エチルエステル (1 ml) を加えて 3 時間攪拌した後に、析出物を濾取し、2- { [1- (3, 5-ジクロロ-2-ヒドロキシ-ベンジル) -ピペリジン-4-イルメチル] -アミノ} -1H-ベンズイミダゾール-4-カルボン酸を得た。LC-MS により同定した。収量 802.6 mg、収率 83.5%、 $[M+1] = 449.1$ 。

[実施例 1-4-18]

2- { [1- (3, 5-ジクロロ-2-ヒドロキシ-ベンジル) -ピペリジン-4-イルメチル] -アミノ} -1H-ベンズイミダゾール-4-カルボン酸イソプロピルアミドの合成

2- { [1- (3, 5-ジクロロ-2-ヒドロキシ-ベンジル) -ピペリジン-4-イルメチル] -アミノ} -1H-ベンズイミダゾール-

4-カルボン酸 (30.0 mg、0.0668 mmol) を、ジメチルホルムアミド (0.50 ml) に懸濁させた。これに1-ヒドロキシベンゾトリアゾール-水和物 (30.6 mg、0.200 mmol)、イソプロピルアミン (11.8 mg、0.200 mmol)、及びジイソプロピルカルボジイミド (30.8  $\mu$ l、0.200 mmol) を加え、40℃で終夜攪拌した。反応液にメタノール (2 ml) を加えて、10分間攪拌した後に、反応液をSCX (ボンドエルトSCX500 MG) に付し、メタノールでSCXを洗浄した。2規定アンモニアメタノール溶液で溶出後、溶媒を減圧下に留去し、残渣を得た。残渣を分取HPLCにより精製して、2- { [1- (3, 5-ジクロロ-2-ヒドロキシ-ベンジル) -ピペリジン-4-イルメチル] -アミノ } -1H-ベンズイミダゾール-4-カルボン酸イソプロピルアミドを得た。LC-MSにより同定した。

収量 25.6 mg、収率 78.1%、純度 97.3%、 $[M+1] = 490.1$

[実施例 1-4-19 から実施例 1-4-30]

化合物番号 1-4-19 から 1-4-30 の化合物は、実施例 1-4-18 に従い、対応する原料より合成した。結果を表 12 に示す。

表 12

化合物 No.1-4-	収量(mg)	収率(%)	MW	M+1
1	10	39	463.4	463.1
2	19	80	428.9	429.1
3	28	100	473.4	473.1
4	18	74	439.5	440.1
5	26	100	428.5	429.2
6	28	100	431.5	432.2
7	28	100	434.6	435.1
8	24	98	406.5	407.2



9	294	44	447.4	447.1
10	9	41	472.0	472.2
11	11	42	516.4	518.1(Br)
12	17	74	482.5	483.2
13	12	49	506.4	506.1
14	6	27	471.6	472.2
15	10	43	474.6	475.2
16	14	59	477.6	478.2
17	22	96	449.6	450.2
18	26	78	490.4	490.1
19	18	56	476.4	476.1
20	24	68	520.5	520.2
21	23	66	518.4	518.1
22	4	22	517.5	517.3
23	9	51	503.5	503.3
24	13	67	575.5	575.3
25	2	12	518.4	518.3
26	21	116	518.4	518.3
27	11	62	490.4	490.2
28	11	61	522.5	522.3
29	13	69	536.5	536.3
30	7	84	475.4	475.2

[参考例 1-5-1]

3, 4-ジアミノ安息香酸エチルエステルの合成

3, 4-ジアミノ安息香酸 (2.003 g、13.17 mmol) 及びトリフェニルホスフィン (4.248 g、16.20 mmol) をトルエン (20 ml) とテトラヒドロフラン (10 ml) に懸濁させた。エタノール (2 ml) を加えて得られた茶褐色懸濁液に、アゾジカルボン酸ジイソプロピル (2.5 ml、9.96 mmol) を滴下し、室温で3.5時間攪拌した。さらにアゾジカルボン酸ジイソプロピル (1.

5 ml、5.98 mmol) を滴下して、室温で1時間攪拌し、得られた反応混合物から1規定塩酸(100 ml×2回)により抽出し、水層を酢酸エチルエステル50 mlで洗浄した。水層へ2規定水酸化ナトリウム水溶液を加えて、pH 11以上とした後、析出物を酢酸エチルエステル(100 ml×2回)抽出した。有機層を飽和食塩水(50 ml)で洗浄し、無水硫酸ナトリウム上で終夜乾燥させた。乾燥剤の濾別、濾液の濃縮の後、3,4-ジアミノ安息香酸エチルエステルを薄黄色固体として得た。LC-MSにより同定した。

収量1.547 g、収率65%、実測値ESI/MS m/e 181.1 (M+1)。

下記の化合物についても、参考例1-5-1と同様に、対応する原料を使用して合成した。

3,4-ジアミノ安息香酸イソプロピルエステル：収量1.302 g、収率49%

3,4-ジアミノ安息香酸イソブチルエステル：収量2.014 g、収率72%

3,4-ジアミノ安息香酸ベンジルエステル：収量0.331 g、収率10%

3,4-ジアミノ安息香酸シクロヘキシルエステル：収量0.245 g、収率8%

[参考例1-5-2]

2-[(1-tert-ブトキシカルボニル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-5-カルボン酸エチルエステル合成

4-アミノメチル-ピペリジン-1-カルボン酸tert-ブチルエステル(0.394 g、1.84 mmol)を、アセトニトリル(3 ml

1) に溶解した。0℃で、チオカルボニルジイミダゾール (0.340 g、1.91 mmol) とイミダゾール (0.052 g、0.77 mmol) のアセトニトリル溶液 (6 ml) を、3分間かけて滴下した。室温で1時間攪拌後、反応液へ3, 4-ジアミノ安息香酸エチルエステル (0.371 g、2.06 mmol) を加え、50℃で5.5時間攪拌した。更に、ジイソプロピルカルボジイミド (0.32 ml) を加え、50℃で終夜攪拌した。得られた反応混合物へ飽和食塩水を加えて、酢酸エチルエステル (100 ml) で抽出し、有機層を無水硫酸ナトリウム上で終夜乾燥させた。乾燥剤の濾別、濾液の濃縮の後に得られた茶褐色油状物を、シリカゲルカラムクロマトグラフィー (ジクロロメタン/メタノール=49/1→19/1) にて精製し、黄色アモルファス状固体の2-[(1-tert-ブトキシカルボニル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-5-カルボン酸エチルエステルを得た。

収量0.838 g、収率%、実測値ESI/MS m/e 403.2 (M+1)。

[参考例1-5-3]

2-[(ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-5-カルボン酸エチルエステルの合成

2-[(1-tert-ブトキシカルボニル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-5-カルボン酸エチルエステルをテトラヒドロフラン (2 ml) に溶解し、4規定塩化水素/1, 4-ジオキサン溶液 (3 ml) を加えた。不溶物が析出したため、エタノール (5 ml) を加えて溶解し、室温で終夜攪拌した。反応液を濃縮して、赤色アモルファス状固体の2-[(ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-5-カルボン酸エチル

エステルを得た。LC-MSにより同定した。

収量 0.942 g、収率 100%、実測値ESI/MS m/e 303.1 (M+1)。

[実施例 1-5-1]

2- { [1- (3, 5-ジクロロ-2-ヒドロキシベンジル) -ピペリジン-4-イルメチル] -アミノ} -1H-ベンズイミダゾール-5-カルボン酸エチルエステルの合成

2- [ (ピペリジン-4-イルメチル) -アミノ] -1H-ベンズイミダゾール-5-カルボン酸エチルエステル (0.1 mmol) のジメチルホルムアミド-酢酸 (10:1) 溶液 (1.0 ml) に、3, 5-ジクロロ-2-ヒドロキシベンズアルデヒド (0.3 mmol) とナトリウムトリアセトキシボロヒドリド (0.3 mmol) を加え、室温で終夜攪拌した。反応溶液にメタノール (1.0 ml) を加え反応を停止し、1時間攪拌後、溶液をSCX (ボンドエルトSCX 500 MG) に付した。メタノール、続いてクロロホルム/メタノール (1/1) 混合溶液で、SCXを洗浄後、0.5規定アンモニアジオキサン溶液で溶出した。溶媒を減圧下に留去し、得られた残渣を分取HPLCに付し、2- { [1- (3, 5-ジクロロ-2-ヒドロキシベンジル) -ピペリジン-4-イルメチル] -アミノ} -1H-ベンズイミダゾール-5-カルボン酸エチルエステル得た。LC-MSにより同定した。

収量 1.6 mg、収率 3.4%、純度 98%、実測値ESI/MS m/e 477.1 (M+1)。

[実施例 1-5-2 から実施例 1-5-8]

化合物番号 1-5-2 から 1-5-8 の化合物は、参考例 1-5-1 から参考例 1-5-3、及び実施例 1-5-1 に従い、対応する原料より合成した。結果を表 13 に示す。

## [参考例 1-5-4]

## 3, 4-ジアミノ安息香酸メチルエステルの合成

3, 4-ジアミノ安息香酸 (25.0 g、164 mmol) のメタノール溶液 (164 ml) に、0℃でゆっくりと塩化チオニル (13.0 ml、180 mmol) を滴下した。室温で終夜攪拌後、更に80℃で終夜攪拌した。反応溶液を室温まで冷却し、析出した固体を濾別しメタノールで洗浄した。濾液は減圧下に濃縮して得られた固体を濾別し、メタノールで洗浄した。得られた固体全てを減圧下60℃で乾燥させ、3, 4-ジアミノ安息香酸メチルエステルを得た。NMRにより同定した。

収量 31.16 g、収率 79%。

$^1\text{H-NMR}$  (270 MHz,  $\text{CDCl}_3$ ) : 3.76 (s, 3H), 6.85 (d, 1H,  $J=8.6\text{ Hz}$ ), 7.63 (dd, 1H,  $J=1.9, 8.6\text{ Hz}$ ), 7.78 (d, 1H,  $J=1.9\text{ Hz}$ ) .

## [実施例 1-5-9 から実施例 1-5-13]

化合物番号 1-5-9 から 1-5-13 の化合物は、参考例 1-5-4、参考例 1-5-2、参考例 1-5-3、及び実施例 1-5-1 に従い対応する原料より合成した。結果を表 13 に示す。

## [参考例 1-5-5]

## 4-メチルアミノ-3-ニトロ-安息香酸メチルエステルの合成

4-フルオロ-3-ニトロ-安息香酸メチルエステル (507.3 mg、2.55 mmol) をテトラヒドロフラン (1 ml) に溶解し、氷浴中でメチルアミン (2.0 M テトラヒドロフラン溶液、2.55 ml、5.09 mmol) を加え、室温で終夜攪拌した。反応液を減圧濃縮して、酢酸エチルエステル (20 ml) に溶解し、飽和炭酸水素ナトリウム水溶液及び飽和食塩水で洗浄した後に、無水硫酸マグネシウムで乾

4-アミノ-3-ニトロ-安息香酸メチルエステル (1.03 g、5.25 mmol) をテトラヒドロフラン (50 ml) に溶解し、ナトリウムビス (トリメチルシリル) アミド (1.0 M テトラヒドロフラン溶液、10.5 ml、10.5 mmol) を加え、室温で15分間攪拌した。これに二炭酸ジブチル (1.44 ml、6.30 mmol) のテトラヒドロフラン溶液 (10 ml) を滴下して、室温で1時間攪拌した。反応液を減圧濃縮し、残渣に1規定塩酸を加えて、pH 約6に調製した。これを酢酸エチルエステル (100 ml × 3回) で抽出し、得られた有機層を飽和食塩水で洗浄した後に、無水硫酸マグネシウムで乾燥させた。減圧濃縮後の残渣をシリカゲルカラムクロマトグラフィー (n-ヘキサン/酢酸エチルエステル = 9/1) で精製して、4-tert-ブトキシカルボニルアミノ-3-ニトロ-安息香酸メチルエステルを得た。LC-MSにより同定した。

収量 1.11 g、収率 71.4%、 $[M+1] = 297.1$ 。

[参考例 1-5-8]

3-アミノ-4-tert-ブトキシカルボニルアミノ-安息香酸メチルエステルの合成

4-tert-ブトキシカルボニルアミノ-3-ニトロ-安息香酸メチルエステル (1.11 g、3.75 mmol) を、酢酸エチルエステルメタノール (1:1) (30 ml) に溶解した。この水溶液に窒素雰囲気下で10%パラジウム-カーボン粉末 (200 mg、5 mol%) を加え、水素雰囲気下で終夜攪拌した。反応液をセライト濾過し、濾液を減圧濃縮して3-アミノ-4-tert-ブトキシカルボニルアミノ-安息香酸メチルエステルを得た。LC-MSにより同定した。

収量 924.1 mg、収率 92.3%、 $[M+1] = 267.3$ 。

[参考例 1-5-9]

4-tert-ブトキシカルボニルアミノ-3-(2-ニトロベンゼンスルホニルアミノ)-安息香酸メチルエステルの合成

3-アミノ-4-tert-ブトキシカルボニルアミノ-安息香酸メチルエステル (817.3 mg, 3.07 mmol) をジクロロメタン (10 ml) に溶解し、氷浴下でピリジン (0.373 ml, 4.60 mmol) 及び2-ニトロベンゼンスルホニルクロリド (815 mg, 3.68 mmol) を加え、室温で4時間攪拌した。ピリジン (0.050 ml) 及び2-ニトロベンゼンスルホニルクロリド (135 mg) を加え、さらに2時間攪拌した。反応液を減圧濃縮して、水 (30 ml) を加えた後に、酢酸エチルエステル (20 ml × 3回) で抽出した。得られた有機層を飽和食塩水で洗浄後、無水硫酸マグネシウムで乾燥させた。減圧濃縮後に結晶化した残渣を、n-ヘキサン-酢酸エチルエステル (4:1) に懸濁した後に、濾取、乾燥させて4-tert-ブトキシカルボニルアミノ-3-(2-ニトロベンゼンスルホニルアミノ)-安息香酸メチルエステルを得た。LC-MSにより同定した。収量 1.23 g、収率 88.7%。

[参考例 1-5-10]

4-tert-ブトキシカルボニルアミノ-3-[メチル-(2-ニトロベンゼンスルホニル)-アミノ]-安息香酸メチルエステルの合成

4-tert-ブトキシカルボニルアミノ-3-(2-ニトロベンゼンスルホニルアミノ)-安息香酸メチルエステル (1.23 g, 2.73 mmol) をジメチルホルムアミド (10 ml) に溶解し、氷浴中で炭酸カリウム (1.13 g, 8.16 mmol) とヨウ化メチル (0.254 ml, 4.09 mmol) を加え、室温で2時間攪拌した。反応液に水 (100 ml) を加え、これを酢酸エチルエステル (40 ml × 4回) で抽出した。得られた有機層を飽和食塩水で洗浄し、無水硫酸

燥させた。これを減圧濃縮して得られた残渣を、メチルアミン-テトラヒドロフラン溶液（2.0 M、3 ml）に溶解し、密封して50℃で5時間攪拌した。反応液を減圧濃縮して酢酸エチルエステル（30 ml）に溶解し、飽和炭酸水素ナトリウム水溶液、飽和食塩水で洗浄した後に、無水硫酸マグネシウムで乾燥させた。これを減圧濃縮して、4-メチルアミノ-3-ニトロ-安息香酸メチルエステルを得た。LC-MSにより同定した。

収量 540 mg、収率 100%、 $[M+1] = 211.1$ 。

[参考例 1-5-6]

3-アミノ-4-メチルアミノ-安息香酸メチルエステルの合成

4-メチルアミノ-3-ニトロ-安息香酸メチルエステル（540 mg、2.5 mmol）を酢酸エチルエステル/メタノール（2:1）（20 ml）に溶解し、窒素雰囲気下で10%パラジウム-カーボン粉末（5 mol%）を加えた。水素雰囲気下で4時間攪拌した後、反応液をセライトを通じて濾過した。濾液を減圧濃縮して、3-アミノ-4-メチルアミノ-安息香酸メチルエステルを得た。LC-MSにより同定した。

収量 441 mg、収率 100%、 $[M+1] = 181.1$ 。

[実施例 1-5-14 から 実施例 1-5-16]

化合物番号 1-5-14 から 1-5-16 の化合物は、参考例 1-5-5、参考例 1-5-6、参考例 1-5-2、参考例 1-5-3、及び実施例 1-5-1 に従い、対応する原料より合成した。結果を表 13 に示す。

[参考例 1-5-7]

4-tert-ブトキシカルボニルアミノ-3-ニトロ-安息香酸メチルエステルの合成



マグネシウムで乾燥させた。減圧濃縮後に結晶化した残渣を乾燥させて 4-tert-ブトキシカルボニルアミノ-3-[メチル-(2-ニトロベンゼンスルホニル)-アミノ]-安息香酸メチルエステルを得た。LC-MSにより同定した。

収率 1.41 g、収率 100%。

[参考例 1-5-11]

4-tert-ブトキシカルボニルアミノ-3-メチルアミノ-安息香酸メチルエステルの合成

4-tert-ブトキシカルボニルアミノ-3-[メチル-(2-ニトロベンゼンスルホニル)-アミノ]-安息香酸メチルエステル (1.41 g、2.73 mmol) をジメチルホルムアミド (10 ml) に溶解し、氷浴中で炭酸カリウム (1.13 g、8.16 mmol) 及びチオフェノール (0.307 ml、2.99 mmol) を加え、室温で 1 時間攪拌した。反応液に水 (100 ml) を加え、これを酢酸エチルエステル (40 ml × 3 回) で抽出した。得られた有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥させた。減圧濃縮後の残渣を、シリカゲルカラムクロマトグラフィー (n-ヘキサン/酢酸エチルエステル = 85/15) で精製して、4-tert-ブトキシカルボニルアミノ-3-メチルアミノ-安息香酸メチルエステルを得た。LC-MSにより同定した。収量 794.3 mg、収率 62.7%、 $[M+1] = 281.1$ 。

[参考例 1-5-12]

4-アミノ-3-メチルアミノ-安息香酸メチルエステルの合成

4-tert-ブトキシカルボニルアミノ-3-メチルアミノ-安息香酸メチルエステル (794.3 mg、2.83 mmol) をメタノール (7.0 ml) に溶解し、氷浴中で 4 規定塩化水素-1,4-ジオキ

サン溶液（3.54 ml、14.3 mmol）を加え、室温で30分間攪拌した。さらに同量の4規定塩化水素-1,4-ジオキサン溶液を加え、40℃で30分間攪拌した。反応液を、氷冷した飽和炭酸水素ナトリウム水溶液に注ぎ、これを酢酸エチルエステル（30 ml×3）で抽出した。得られた有機層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥させた。減圧濃縮後の残渣を、シリカゲルカラムクロマトグラフィー（n-ヘキサン／酢酸エチルエステル＝4／1→3／2→1／1）で精製して、4-アミノ-3-メチルアミノ-安息香酸メチルエステルを得た。LC-MSにより同定した。

収量342.7 mg、収率67.2%、 $[M+1] = 181.1$ 。

[実施例1-5-17から実施例1-5-19]

化合物番号1-5-17から1-5-19の化合物は、参考例1-5-7から参考例1-5-12、参考例1-5-2、参考例1-5-3、及び実施例1-5-1に従い、対応する原料より合成した。結果を表13に示す。

[実施例1-5-20]

2- { [1- (3-フェニル-プロピル) -ピペリジン-4-イルメチル] -アミノ} -1H-ベンズイミダゾール-5-カルボン酸の合成

2- { [1- (3-フェニル-プロピル) -ピペリジン-4-イルメチル] -アミノ} -1H-ベンズイミダゾール-5-カルボン酸メチルエステル（3.2 mmol）をメタノール（10 ml）に懸濁し、4規定水酸化リチウム水溶液（5.4 ml、21.4 mmol）を加えた。反応液を50℃で2時間攪拌した後に、室温に冷却した。これに1規定塩酸を滴下して、pH約6.0に調製した。この水溶液に酢酸エチルエステル（1 ml）を加えて3時間攪拌した後に、析出物を濾取し、2- { [1- (3-フェニル-プロピル) -ピペリジン-4-イルメチル]

－アミノ〕－1H－ベンズイミダゾール－5－カルボン酸を得た。LC－MSにより同定した。

収量 1.01 g、収率 79.9%、純度 98.5%、 $[M+1] = 393.1$ 。

[実施例 1－5－21 から実施例 1－5－22]

化合物番号 1－5－21 から 1－5－22 の化合物は、実施例 1－5－20 に従い、対応する原料より合成した。結果を表 13 に示す。

[実施例 1－5－23]

2－〔（1－ナフタレン－1－イルメチル－ピペリジン－4－イルメチル）－アミノ〕－1H－ベンズイミダゾール－5－カルボン酸（2－ジメチル）－アミドの合成

2－〔（1－ナフタレン－1－イルメチル－ピペリジン－4－イルメチル）－アミノ〕－1H－ベンズイミダゾール－5－カルボン酸（20.0 mg、0.0480 mmol）及び 1－ヒドロキシベンゾトリアゾール－水和物（22.0 mg、0.145 mmol）をテトラヒドロフラン－ジメチルホルムアミド（1：1，0.500 ml）に溶解した。これに、N，N－ジメチルエチレンジアミン（0.0160 ml、0.145 mmol）及び N，N－ジイソプロピルカルボジイミド（0.0220 ml、0.145 mmol）を加え、室温で終夜攪拌した。反応液に水（2 ml）を加えて、10 分間攪拌し、酢酸エチルエステル（1 ml × 3 回）で抽出した。得られた酢酸エチルエステル層を、SCX 固相抽出で精製した後に、HPLC 分取で精製して、2－〔（1－ナフタレン－1－イルメチル－ピペリジン－4－イルメチル）－アミノ〕－1H－ベンズイミダゾール－5－カルボン酸（2－ジメチル）－アミドを得た。LC－MS により同定した。

収量 10.5 mg、収率 45.1%、純度 100%、 $[M+1] = 48$

## 5. 4

[実施例 1-5-24 から実施例 1-5-190]

化合物番号 1-5-24 から 1-5-190 までの化合物は、実施例 1-5-23 に従い、対応する原料より合成した。結果を表 13 に示す。

[参考例 1-5-13]

2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-ベンズイミダゾール-1, 5-ジカルボン酸 1-tert-ブチルエステル 5-メチルエステルの合成

2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-5-カルボン酸メチルエステル (1 g、2.33 mmol) を 1, 4-ジオキサン (25 ml) に溶解し、二炭酸-ジ-tert-ブチル (1017 mg、4.66 mmol) を加え、80℃で 11 時間攪拌した。溶媒を減圧下に留去し、得られた残渣をシリカゲルカラムクロマトグラフィー (ジクロロメタン/メタノール/TEA=85/10/5) により精製し、2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-ベンズイミダゾール-1, 5-ジカルボン酸 1-tert-ブチルエステル 5-メチルエステルを得た。LC-MS により同定した。

収量 1.1 g、収率 96%、LCMS (529.2 m/z M+1)。

[実施例 1-5-191]

{2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-5-イル}-メタノールの合成

窒素気流下で、2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-ベンズイミダゾール-1, 5-ジカ

ルボン酸 1-tert-ブチルエステル 5-メチルエステル (940 mg, 1.78 mmol) を、乾燥テトラヒドロフラン (18 ml) に溶解し、0℃でリチウム水素化アルミニウム (135 mg, 3.56 mmol) を加え、3時間攪拌した。飽和硫酸ナトリウム水溶液を加えた後、溶媒を減圧下に留去した。水が残っていたため、残渣を酢酸エチルエステルに溶解し、飽和食塩水で洗浄後、溶媒を減圧下に留去し、残渣を得た。残渣をシリカゲルカラムクロマトグラフィー (ジクロロメタン/メタノール/TEA=90/5/5) により精製し、{2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-5-イル}-メタノールを得た。収量 822 mg、収率 91%、純度 89.3%、LCMS (401.2 m/z M+1)。

[実施例 1-5-192]

2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-5-カルボアルデヒドの合成

1-ヒドロキシ-1-オキソ-1H-1λ<sup>5</sup>-ベンゾ[d][1,2]ヨードキソール-3-オン (846 mg, 3.02 mmol) のジメチルスルホキシド溶液 (10 ml) を、{2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-5-イル}-メタノール (807 mg, 2.01 mmol) のジメチルスルホキシド溶液 (10 ml) に加え、室温で9時間攪拌した。氷水 (200 ml) に反応溶液を流し込み、室温で30分攪拌後、酢酸エチルエステルを加え、10分間激しく攪拌し抽出を行った。飽和炭酸水素ナトリウム水溶液、飽和食塩水で洗浄後、無水硫酸ナトリウムで乾燥した後、溶媒を減圧下に留去し、得られた残渣をシリカゲ

ルカラムクロマトグラフィー（酢酸エチルエステル／メタノール＝9／1）により精製した。さらに分取HPLCで精製し、2-〔（1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル）-アミノ〕-1H-ベンズイミダゾール-5-カルボアルデヒドを得た。

収量34mg、収率4%、純度100%、LCMS（399.2m/z M+1）。

〔実施例1-5-193〕

2-〔（1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル）-アミノ〕-1H-ベンズイミダゾール-5-カルボニトリルの合成

窒素気流下で、2-〔（1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル）-アミノ〕-1H-ベンズイミダゾール-5-カルボアルデヒド（2.7mg、0.0570mmol）を無水ジメチルホルムアミド（1ml）に溶解し、ヒドロキシルアミン塩酸塩（8mg、0.115mmol）と6規定塩酸一滴を加えた後、80℃で2時間30分攪拌した。5規定水酸化ナトリウム水溶液2滴を加え、酢酸エチルで抽出後、ジクロロメタンで抽出した。有機層を飽和食塩水で洗浄後、無水硫酸ナトリウムで乾燥し、溶媒を減圧下に留去し、残渣を得た。残渣に、無水ジメチルホルムアミド（1ml）と4規定塩化水素／1，4-ジオキサン溶液を9滴加え、100℃で12時間攪拌した。5規定水酸化ナトリウム水溶液で中和後、同様の抽出処理を行い、得られた残渣を薄層シリカゲルクロマトグラフィー（ジクロロメタン／メタノール／トリエチルアミン＝85／10／5）で精製し、2-〔（1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル）-アミノ〕-1H-ベンズイミダゾール-5-カルボニトリルを得た。

収率29%、純度99.3%、収量6.6mgで得た。LCMS（39

6.  $3m/z \quad M+1$  )。

[参考例 1-5-14]

2- [ (1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル) - (2-トリメチルシラニル-エトキシメチル) - アミノ ] - 1- (2-トリメチルシラニル-エトキシメチル) - 1H-ベンズイミダゾール-5-カルボン酸メチルエステルの合成

2- [ (1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル) - アミノ ] - 1H-ベンズイミダゾール-5-カルボン酸メチルエステル (1 g、2.33 mmol) を、窒素気流下で、無水テトラヒドロフラン (30 ml) に溶解し、0℃に冷却した。60%水素化ナトリウム (187 mg、4.89 mmol) を加え、0℃で72分間攪拌した。2- (トリメチルシリル) エトキシメチルクロリド (815.8 mg、4.89 mmol) を加え、0℃で30分攪拌後水を加えた。この溶液を、酢酸エチル続いてジクロロメタンで抽出し、それぞれを飽和食塩水で洗浄後、合わせて無水硫酸ナトリウムで乾燥した。溶媒を減圧下に留去し、得られた残渣をシリカゲルカラムクロマトグラフィー (酢酸エチルエステル/ヘキサン = 2/3 → 3/2 → 1/0) により精製し、2- [ (1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル) - (2-トリメチルシラニル-エトキシメチル) - アミノ ] - 1- (2-トリメチルシラニル-エトキシメチル) - 1H-ベンズイミダゾール-5-カルボン酸メチルエステルを得た。LC-MSにより同定した。

収量 624 mg、収率 39%、純度 95.1%、LCMS ( $689.3 m/z \quad M+1$ )。

[参考例 1-5-15]

[2- [ (1-ナフタレン-1-イルメチル-ピペリジン-4-イルメ

チル) - (2-トリメチルシラニル-エトキシメチル) - アミノ] - 1 - (2-トリメチルシラニル-エトキシメチル) - 1H-ベンズイミダゾール-5-イル] - メタノールの合成

窒素気流下で、2 - [(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル) - (2-トリメチルシラニル-エトキシメチル) - アミノ] - 1 - (2-トリメチルシラニル-エトキシメチル) - 1H-ベンズイミダゾール-5-カルボン酸メチルエステル (624 mg、0.91 mmol) を無水テトラヒドロフラン (10 ml) に溶解し、0℃でリチウム水素化アルミニウム (72.4 mg、1.82 mmol) を加え、そのまま2時間攪拌した。飽和硫酸ナトリウム水溶液を加えた後、酢酸エチル続いてジクロロメタンで抽出した。それぞれを飽和食塩水で洗浄後、合わせて、無水硫酸ナトリウムで乾燥した。溶媒を減圧下に留去し、[2 - [(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル) - (2-トリメチルシラニル-エトキシメチル) - アミノ] - 1 - (2-トリメチルシラニル-エトキシメチル) - 1H-ベンズイミダゾール-5-イル] - メタノールを得た。LC-MSにより同定した。

収量 568 mg、収率 95%、純度 89.4%、LCMS (661.4 m/z M+1)。

#### [参考例 1-5-16]

2 - [(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル) - (2-トリメチルシラニル-エトキシメチル) - アミノ] - 1 - (2-トリメチルシラニル-エトキシメチル) - 1H-ベンズイミダゾール-5-カルボアルデヒドの合成

[2 - [(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル) - (2-トリメチルシラニル-エトキシメチル) - アミノ] -



1-〔2-トリメチルシラニル-エトキシメチル〕-1H-ベンズイミダゾール-5-イル〕-メタノール(467mg、0.71mmol)のジメチルスルホキシド溶液(5ml)を、1-ヒドロキシ-1-オキソ-1H-1 $\lambda^5$ -ベンゾ[d][1,2]ヨードキソール-3-オン297mg(1.06mmol)のジメチルスルホキシド溶液(5ml)に加え、室温で18時間攪拌した。氷水(200ml)に反応溶液を流し込み、室温で30分攪拌後、酢酸エチルエステルを加え10分間激しく攪拌し、抽出を行った。飽和炭酸水素ナトリウム水溶液、続いて飽和食塩水で洗浄後、無水硫酸ナトリウムで乾燥した後、溶媒を減圧下に留去し、2-〔(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-(2-トリメチルシラニル-エトキシメチル)-アミノ〕-1-〔2-トリメチルシラニル-エトキシメチル〕-1H-ベンズイミダゾール-5-カルボアルデヒドを得た。

収量475mg、収率100%、純度83.2%、LCMS(659.3m/z M+1)。

[参考例1-5-17]

1-〔2-〔(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-(2-トリメチルシラニル-エトキシメチル)-アミノ〕-1-〔2-トリメチルシラニル-エトキシメチル〕-1H-ベンズイミダゾール-5-イル〕-プロパン-1-オルの合成

窒素気流下に、2-〔(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-(2-トリメチルシラニル-エトキシメチル)-アミノ〕-1-〔2-トリメチルシラニル-エトキシメチル〕-1H-ベンズイミダゾール-5-カルボアルデヒド(86mg、0.131mmol)を無水テトラヒドロフラン(1.2ml)に溶解し、0℃でエチルマグネシウムブロミド(0.26ml、1Mテトラヒドロフラン

溶液)を加え、添加後室温で13分間攪拌した。飽和塩化アンモニウム水溶液を加えた後、酢酸エチルエステルで抽出を行った。有機層を飽和食塩水で洗浄した後、硫酸ナトリウムで乾燥し、次に溶媒を減圧下に留去し、1-[2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-(2-トリメチルシラニル-エトキシメチル)-アミノ]-1-(2-トリメチルシラニル-エトキシメチル)-1H-ベンズイミダゾール-5-イル]-プロパン-1-オルを得た。

収量92.5mg、収率100%、純度88%、LCMS(689.3m/z M+1)。

[実施例1-5-194]

1-{2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズイミダゾール-5-イル}-プロパン-1-オルの合成

1-[2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-(2-トリメチルシラニル-エトキシメチル)-アミノ]-1-(2-トリメチルシラニル-エトキシメチル)-1H-ベンズイミダゾール-5-イル]-プロパン-1-オル(50mg、0.073mmol)を無水ジメチルホルムアミド(2ml)に溶解し、フッ化テトラブチルアンモニウム(0.5ml、1.0Mテトラヒドロフラン溶液)を加え、100℃で13時間攪拌した。酢酸エチルエステル、水を加えた後、水層をpH11にして、酢酸エチルエステルで抽出した。有機層を飽和食塩水で洗浄し、次に無水硫酸ナトリウムによる乾燥を行い、溶媒を減圧下に留去し、得られた残渣を薄層シリカゲルクロマトグラフィー(酢酸エチルエステル/メタノール=4/1)で精製した。さらにHPLC分取により精製し、1-{2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ]-1H-ベンズ

イミダゾール-5-イル}-プロパン-1-オールを得た。

収量 1.08 mg、収率 3%、純度 100%、LCMS (429.2 m/z M+1)。

[参考例 1-5-18]

1-[2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-(2-トリメチルシラニル-エトキシメチル)-アミノ]-1-(2-トリメチルシラニル-エトキシメチル)-1H-ベンズイミダゾール-5-イル]-プロパン-1-オンの合成

1-[2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-(2-トリメチルシラニル-エトキシメチル)-アミノ]-1-(2-トリメチルシラニル-エトキシメチル)-1H-ベンズイミダゾール-5-イル]-プロパン-1-オール (72 mg、0.10 mmol) のジメチルスルホキシド溶液 (1 ml) を、1-ヒドロキシ-1-オキソ-1H-1λ<sup>5</sup>-ベンゾ[d][1,2]ヨードキソール-3-オン (44 mg、0.157 mmol) のジメチルスルホキシド溶液 (1 ml) に加え、室温で 18 時間攪拌した。氷水 (50 ml) に反応溶液を流し込み、室温で 30 分攪拌後、酢酸エチルエステルを加え、10 分間激しく攪拌し抽出を行った。飽和炭酸水素ナトリウム水溶液、続いて飽和食塩水で洗浄後、無水硫酸ナトリウムで乾燥した後、溶媒を減圧下に留去し、1-[2-[(1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-(2-トリメチルシラニル-エトキシメチル)-アミノ]-1-(2-トリメチルシラニル-エトキシメチル)-1H-ベンズイミダゾール-5-イル]-プロパン-1-オンを得た。

収量 64 mg、収率 89%、純度 92.8%、LCMS (687.4 m/z M+1)。

## [実施例 1-5-195]

1- { 2- [ (1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ] -1H-ベンズイミダゾール-5-イル} -プロパン-1-オンの合成

1- [ 2- [ (1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)- (2-トリメチルシラニル-エトキシメチル)-アミノ] -1- (2-トリメチルシラニル-エトキシメチル)-1H-ベンズイミダゾール-5-イル] -プロパン-1-オン (32 mg、0.047 mmol) を、無水ジメチルホルムアミド (1 ml) に溶解し、フッ化テトラブチルアンモニウム (0.8 ml、1.0 M テトラヒドロフラン溶液) と水 (5  $\mu$ l) を加え、100℃で2時間30分間攪拌した。水と酢酸エチルエステルを加え、酢酸エチルエステル抽出を行った。有機層を飽和食塩水で洗浄し、次に無水硫酸ナトリウムによる乾燥を行い、溶媒を減圧下に留去し得られた残渣を、薄層シリカゲルクロマトグラフィー (ジクロロメタン/メタノール/TEA=85/10/1) により精製した。さらにHPLC分取と薄層シリカゲルクロマトグラフィー (ジクロロメタン/メタノール=8/2) により精製し、1- { 2- [ (1-ナフタレン-1-イルメチル-ピペリジン-4-イルメチル)-アミノ] -1H-ベンズイミダゾール-5-イル} -プロパン-1-オンを得た。

収量 2.04 mg、収率 10%、純度 100%、LCMS (427.2 m/z M+1)。

## [実施例 1-5-196 と実施例 1-5-197]

化合物番号 1-5-196 と 1-5-197 の化合物は、実施例 1-5-195 に従い、対応する原料より合成した。結果を表 13 に示す。

表 13

化合物 No.1-5-	収量(mg)	収率(%)	MW	M+1
1	2	3	477.4	477.1
2	14	31	442.9	443.1
3	15	35	442.6	443.2
4	12	29	420.6	421.2
5	1	2	491.4	491.2
6	4	9	457.0	457.2
7	11	26	456.6	457.2
8	21	52	434.6	435.2
9	48	92	428.5	429.1
10	51	100	406.5	407.2
11	8	20	463.4	463.1
12	13	36	439.5	440.1
13	500	58	434.6	435.1
14	19	28	477.4	477.1
15	41	100	442.6	443.2
16	45	100	420.6	421.2
17	6	24	477.4	477.1
18	23	99	442.6	443.2
19	24	100	420.6	421.2
20	1010	80	392.5	393.1
21	994	93	417.5	418.1
22	458	67	459.3	459.4
23	11	45	484.6	485.4
24	10	43	498.6	499.4
25	39	100	556.7	557.5
26	13	53	499.6	500.3
27	13	57	471.6	472.3
28	12	51	503.6	504.4
29	4	16	517.7	518.4
30	17	51	455.6	456.4
31	12	35	469.6	470.3
32	8	23	483.7	484.4

33	3	10	469.6	470.4
34	7	18	499.6	500.4
35	17	52	457.6	458.4
36	15	43	471.6	472.3
37	6	19	456.6	457.4
38	25	100	433.6	434.2
39	10	43	462.6	463.2
40	4	16	476.6	477.2
41	7	27	534.7	535.3
42	9	36	477.6	478.2
43	8	36	435.6	436.2
44	29	100	477.6	478.2
45	27	100	449.6	450.2
46	29	100	481.6	482.3
47	29	100	495.7	496.3
48	14	61	458.6	459.2
49	9	39	487.7	488.3
50	11	47	502.6	503.3
51	10	42	474.6	475.2
52	9	39	506.7	507.2
53	10	38	520.7	521.3
54	11	24	456.0	456.2
55	13	27	485.0	485.2
56	8	16	499.0	499.2
57	9	16	557.1	557.2
58	16	32	500.0	500.1
59	10	20	500.0	500.2
60	15	32	472.0	472.2
61	17	34	504.0	504.1
62	19	37	518.1	518.2
63	21	48	440.0	440.2
64	8	17	469.0	469.1
65	23	48	483.0	483.2

66	19	35	541.1	541.2
67	9	19	484.0	484.2
68	2	5	442.0	442.1
69	11	23	484.0	484.1
70	26	53	488.0	488.2
71	29	58	502.1	502.2
72	21	46	456.0	456.1
73	14	31	457.6	458.2
74	15	34	435.6	436.2
75	5	11	460.6	461.2
76	14	31	458.0	458.1
77	11	25	442.0	442.1
78	14	32	441.6	442.2
79	12	29	419.6	420.2
80	10	22	444.6	445.2
81	15	34	442.0	442.2
82	10	23	426.0	426.1
83	9	21	427.5	428.2
84	10	25	405.5	406.2
85	2	5	430.6	431.2
86	10	23	427.9	428.1
87	23	56	411.9	412.2
88	12	45	522.5	522.0
89	13	52	518.4	518.1
90	6	29	474.4	474.0
91	11	47	503.5	503.1
92	10	41	517.5	517.1
93	6	26	518.4	518.1
94	5	20	490.4	490.0
95	11	42	575.5	575.1
96	9	37	536.5	536.0
97	18	60	475.4	475.2
98	24	92	490.4	490.0

99	12	28	476.4	476.0
100	8	15	557.5	557.3
101	5	10	543.5	543.3
102	5	9	526.5	526.3
103	5	8	538.5	538.1
104	5	10	516.5	516.3
105	5	10	542.6	542.3
106	8	16	514.4	514.2
107	2	5	486.4	486.2
108	4	9	478.4	484.3
109	4	7	544.5	544.2
110	11	20	546.5	546.3
111	3	5	560.5	560.3
112	10	20	517.5	517.2
113	12	22	530.5	531.3
114	10	21	471.4	471.1
115	3	5	532.5	532.3
116	7	14	472.4	473.3
117	10	18	516.5	516.3
118	9	18	502.5	502.0
119	7	14	543.5	543.3
120	3	6	486.4	486.3
121	4	8	502.5	502.3
122	10	19	528.5	528.2
123	7	14	502.5	502.0
124	9	18	488.5	488.2
125	7	13	570.6	570.2
126	33	70	472.4	473.3
127	20	38	542.6	543.3
128	33	60	545.6	545.3
129	24	47	516.5	517.3
130	31	56	545.6	545.4
131	28	55	502.5	503.3



132	32	70	460.4	461.2
133	23	45	518.5	519.3
134	25	48	530.5	531.3
135	23	45	502.5	503.3
136	23	44	518.5	519.3
137	19	37	520.5	521.3
138	16	30	528.5	529.3
139	19	36	528.5	529.3
140	33	70	470.4	471.3
141	19	34	556.6	557.4
142	15	30	517.5	517.3
143	17	34	488.5	489.3
144	20	41	488.5	489.3
145	20	41	488.5	489.3
146	7	14	516.5	517.3
147	22	41	531.5	529.3
148	17	30	559.5	559.3
149	16	34	474.4	475.2
150	21	41	500.5	501.3
151	15	29	514.5	515.3
152	9	18	504.5	505.3
153	34	58	573.6	573.4
154	28	56	504.5	504.3
155	35	61	571.6	571.4
156	31	59	529.5	529.3
157	28	48	587.6	587.4
158	20	36	546.5	547.3
159	3	6	500.5	500.2
160	2	3	502.4	502.3
161	2	4	528.5	528.2
162	1	2	516.5	516.3
163	1	2	532.5	532.3
164	2	4	517.5	517.3

165	36	71	503.4	503.3
166	19	38	489.4	489.2
167	6	10	550.5	550.3
168	3	6	503.4	503.3
169	2	4	485.4	485.2
170	1	2	502.5	502.1
171	2	3	508.9	508.1
172	4	6	559.6	559.3
173	3	6	502.5	502.0
174	22	37	589.6	589.4
175	21	35	603.6	603.3
176	5	10	523.5	523.2
177	6	12	523.5	523.2
178	5	10	523.5	523.2
179	5	11	504.5	504.3
180	7	14	508.5	508.2
181	2	3	520.9	520.2
182	2	3	488.5	488.2
183	4	7	538.5	538.1
184	821	100	400.5	401.2
185	34	4	398.5	399.2
186	7	29	395.5	396.3
187	1	3	428.6	429.2
188	2	9	426.6	427.2
189	4	1	412.5	413.2
190	3	1	440.6	441.2
191	822	91	400.5	401.2
192	34	4	398.6	399.2
193	7	29	395.6	396.3
194	1	3	428.5	429.2
195	2	10	426.6	427.2
196	7	18	499.0	500.4
197	871	41	428.0	429.2

## [実施例 1-6-1]

[1-(3, 4-ジクロロベンジル)-ピペリジン-4-イルメチル]  
]- (1-エチル-1H-ベンズイミダゾール-2-イル)-アミンの  
合成

(1H-ベンズイミダゾール-2-イル)-[1-(3, 4-ジクロ  
ロベンジル)-ピペリジン-4-イルメチル]-アミン (20 mg、  
0.05 mmol) をジメチルホルムアミド (1 ml) に溶かし、臭素  
化エチル (0.075 mmol) と水素化ナトリウム (0.1 mmol)  
を加え、室温で3時間30分攪拌した。反応溶液に氷、希塩酸を加え  
反応を停止し、溶液をSCX (ボンドエルトSCX500MG) に付  
した。SCXをメタノールで洗浄後、2規定アンモニアメタノール溶液  
で溶出し、得られた溶出液を減圧下に留去した。残渣を薄層シリカゲル  
クロマトグラフィー (ヘキサン/酢酸エチルエステル/ジクロロメタン  
/メタノール=60/25/10/5) により精製し、[1-(3, 4  
-ジクロロベンジル)-ピペリジン-4-イルメチル]- (1-エチ  
ル-1H-ベンズイミダゾール-2-イル)-アミンと[1-(3, 4  
-ジクロロベンジル)-ピペリジン-4-イルメチル]-エチル- (1  
-エチル-1H-ベンズイミダゾール-2-イル)-アミンを得た。  
LC-MSにより同定した。

収量 5.8 mg、収率 28%、純度 100%、実測値ESI/MS m  
/e 417.0 (M+1)。

## [実施例 1-6-2]

化合物番号 1-6-2 の化合物、[1-(3, 4-ジクロロベンジ  
ル)-ピペリジン-4-イルメチル]-エチル- (1-エチル-1H-  
ベンズイミダゾール-2-イル)-アミンは、実施例 1-6-1 に従い

、対応する原料より合成した。

収量 7. 7 mg、収率 35%、純度 100%、実測値 ESI/MS m/e 445. 1 (M+1)。

[実施例 1-6-3 から実施例 1-6-15]

化合物番号 1-6-3 から 1-6-15 の化合物は、実施例 1-6-1 に従い、対応する原料より合成した。結果を表 14 に示す。

表 14

化合物 No.1-6-	収量(mg)	収率(%)	MW	M+1
1	6	28	417.4	417.0
2	8	35	445.4	445.1
3	15	52	569.6	569.3
4	6	23	479.5	479.3
5	6	20	557.6	557.2
6	6	26	473.5	473.1
7	1	3	625.7	625.4
8	9	34	507.5	507.3
9	2	7	461.4	461.2
10	6	24	517.5	517.2
11	3	13	446.4	446.2
12	3	15	460.4	460.1
13	8	33	461.4	461.2
14	4	20	442.4	443.1
15	6	24	489.4	489.2

# 《キナゾリノン誘導体の合成 その 1》

[参考例 2-1]

{1-[(3, 4-ジクロロフェニル)メチル]-4-ピペリジル}メチルアミンの合成

4-アミノメチルピペリジン (13. 7 g、120 mmol) をアセ

トニトリル (200 ml) に溶解し、炭酸カリウム (11.057 g、80 mmol) と 3,4-ジクロロベンジルクロリド (7.818 g、40 mmol) を加えて、60℃で終夜攪拌した。反応終了後、ろ別を行い、溶媒を留去した。シリカゲルカラムクロマトグラフィー (ジクロロメタン/メタノール/トリエチルアミン=90/5/5) により精製し、{1-[(3,4-ジクロロフェニル)メチル]-4-ピペリジル}メチルアミンを得た。LC-MS測定により同定した。

収量 10.8 g、収率定量的、 $M+1=273.1$ 。

[参考例 2-2]

N-{[(1-[(3,4-ジクロロフェニル)メチル](4-ピペリジル))メチル)アミノ]チオキソメチル} (フルオレン-9-イルメトキシ)カルボキシアミドの合成

{1-[(3,4-ジクロロフェニル)メチル]-4-ピペリジル}メチルアミン (1325 mg、4.84 mmol) をテトラヒドロフラン (20 ml) に溶解し、FmocNCS (9-フルオレニルメトキシカルボニルイソチオシアネート) (1498 mg、5.32 mmol) を加えて、室温で終夜攪拌した。反応終了後、濃縮し、シリカゲルカラムクロマトグラフィー (ヘキサン/酢酸エチル=85/15) により精製し、N-{[(1-[(3,4-ジクロロフェニル)メチル](4-ピペリジル))メチル)アミノ]チオキソメチル} (フルオレン-9-イルメトキシ)カルボキシアミドを得た。LC-MS測定により同定した。

収量 2624 mg、収率 98%、 $M+1=554.1$ 。

[参考例 2-3]

アミノ[(1-[(3,4-ジクロロフェニル)メチル](4-ピペリジル))メチル)アミノ]メタン-1-チオンの合成

N- { [ ( { 1 - [ ( 3 , 4 - ジクロロフェニル ) メチル ] ( 4 - ピペリジル ) } メチル ) アミノ ] チオキソメチル } (フルオレン-9-イルメトキシ)カルボキシアミド (553 mg、1 mmol) を DMF (4 ml) に溶解し、ピペリジン (0.989 ml、10 mmol) を加えて、室温で終夜撹拌した。反応終了後、水 (20 ml) を加えて、酢酸エチル (20 ml × 3 回) で抽出した。抽出した有機層を水 (100 ml × 2 回)、続いて飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、ろ別し濃縮した。シリカゲルカラムクロマトグラフィー (酢酸エチル/メタノール = 1/0 → 4/1) により精製し、アミノ [ ( { 1 - [ ( 3 , 4 - ジクロロフェニル ) メチル ] ( 4 - ピペリジル ) } メチル ) アミノ ] メタン-1-チオンを得た。LC-MS 測定により同定した。収量 284 mg、収率 86%、 $M+1=332.0$ 。

[参考例 2-4]

( { 1 - [ ( 3 , 4 - ジクロロフェニル ) メチル ] ( 4 - ピペリジル ) } メチル ) (イミノメチルチオメチル) アミンの合成

アミノ [ ( { 1 - [ ( 3 , 4 - ジクロロフェニル ) メチル ] ( 4 - ピペリジル ) } メチル ) アミノ ] メタン-1-チオン (148 mg、0.446 mmol) をテトラヒドロフラン (5 ml) に溶解し、ヨウ化メチル (71 mg、0.491 mmol) を加えて、室温で終夜撹拌した。反応終了後、濃縮し、デシケーター中で減圧乾燥し、( { 1 - [ ( 3 , 4 - ジクロロフェニル ) メチル ] ( 4 - ピペリジル ) } メチル ) (イミノメチルチオメチル) アミンを得た。LC-MS 測定により同定した。

収量 211 mg、収率定量的、 $M+1=346.1$ 。

[実施例 2-1]

2 - [ ( { 1 - [ ( 3 , 4 - ジクロロフェニル ) メチル ] - 4 - ピペリ

ジル} メチル) アミノ] ヒドロキナゾリン-4-オンの合成

( { 1 - [ ( 3 , 4 - ジクロロフェニル ) メチル ] ( 4 - ピペリジル ) } メチル ) ( イミノメチルチオメチル ) アミン ( 7 0 m g , 0 . 1 4 8 m m o l ) とイサト酸無水物 ( 2 7 m g , 0 . 1 6 3 m m o l ) を D M F ( 1 . 5 m l ) に溶解し、8 0 ℃で2時間攪拌した。2 N 水酸化ナトリウム水溶液 ( 1 m l ) を加えて、反応を停止した。水 ( 1 5 m l ) を加え、酢酸エチル ( 1 5 m l × 3 回 ) で抽出した。抽出した有機層を水 ( 5 0 m l × 2 回 ) 、続いて飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、ろ別し濃縮した。シリカゲルカラムクロマトグラフィー ( 酢酸エチル / メタノール = 1 / 0 → 4 / 1 ) により精製し、2 - [ ( { 1 - [ ( 3 , 4 - ジクロロフェニル ) メチル ] - 4 - ピペリジル } メチル ) アミノ ] ヒドロキナゾリン-4-オンを得た。LC-MS測定により同定した。

収量 2 7 m g 、収率 4 4 % 、 $M+1=417.1$ 。

#### [実施例 2-2 ~ 2-3]

化合物番号 2-2 から 2-3 の化合物は、それぞれ対応する反応物を用いて、実施例 2-1 の方法に従い合成した。結果を表 1 5 に示す。

#### 《キナゾリノン誘導体の合成 その2》

##### [参考例 2-5]

2-メルカプト-4 ( 3 H ) キナゾリノン-4-オンの合成

2-メルカプト-4 ( 3 H ) キナゾリノン ( 2 5 m m o l , 4 . 4 5 g ) を水 ( 1 0 0 m l ) と 2 N - N a O H ( 1 . 1 e q , 1 4 m l ) の混合水溶液に溶解し、MeI ( 1 . 1 e q , 1 . 7 2 m l ) を加えて、室温で2時間30分攪拌した。反応終了後、ろ別し、水 1 8 0 m l を加えて洗浄し、減圧下、デシケーター中で4時間乾燥した。LC-MSにより同定した。

収率定量的、収量 5.5 g、 $M+1=192.9$ 。

〔実施例 2-4〕

2-（{[1-（ナフチルメチル）-4-ピペリジル]メチル}アミノ）ヒドロキナゾリン-4-オンの合成

[1-（ナフチルメチル）-4-ピペリジル]メチルアミン（4.4 mmol, 1122 mg）を DMA（15 mL）に溶解し、NEt<sub>3</sub>（1.5 eq, 920  $\mu$ L）、2-メチルチオヒドロキナゾリン-4-オン（2 eq, 1690 mg）を加えた。100℃で終夜攪拌し、反応終了後、酢酸エチル（50 mL×3回）で抽出し、水（150 mL×2回）で洗浄後、硫酸ナトリウムで乾燥した。濃縮後、カラムクロマトグラフィー（Hex/AcOEt=1/9, AcOEt×2）により精製した。LC-MSにより同定した。

収率 10%、収量 159 mg、 $M+1=399.3$ 。

《キナゾリノン誘導体の合成 その3》

[2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩の合成

〔参考例 2-6〕

1-Boc-4-アミノメチルピペリジンの調整

4-アミノメチルピペリジン（10.0 g, 87.6 mmol）をトルエン（175 mL）に溶解し、ベンズアルデヒド（8.90 mL, 87.6 mmol）を加え、Dean-Starkトラップを備えて、1時間加熱還流した。反応液を室温に冷却後、二炭酸ジ-*t*-ブチル（20.1 mL, 87.6 mmol）を4回に分けて1時間で加え、一晚攪拌した。反応液を減圧濃縮した残渣に、氷浴中で硫酸水素カリウム水溶液（1.0 M, 140 mL, 140 mmol）を加えて、2時間攪拌した。この水溶液をジエチルエーテル（100 mL）で洗浄後、1規定



水酸化ナトリウム水溶液を加えて、pH約7に調製した。この水溶液を酢酸エチル（200 mL）で洗浄した後に、1規定水酸化ナトリウム水溶液を加えて、pH約12に調整し、酢酸エチル（100 mL×3回）で抽出した。得られた有機層を飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥させた。これを減圧濃縮、真空乾燥した。LC-MS測定により同定した。

収量16.04 g、収率85%、 $M+23=237.1$ 。

[参考例2-7]

〔（〔フルオレン-9-イルメトキシ〕カルボニルアミノ〕チオキソメチル）アミノ〕メチル〕ピペリジンカルボン酸tert-ブチルエステルの合成

1-Boc-4-アミノメチルピペリジン（2140 mg、10 mmol）をテトラヒドロフラン（25 mL）に溶解し、FmocNCS（3091 mg、11 mmol）を加えて、室温で終夜攪拌した。反応終了後、濃縮し、シリカゲルカラムクロマトグラフィー（ヘキサン／酢酸エチル=85／15→4／1）により精製し、〔（〔フルオレン-9-イルメトキシ〕カルボニルアミノ〕チオキソメチル）アミノ〕メチル〕ピペリジンカルボン酸tert-ブチルエステルを得た。LC-MS測定により同定した。

収量4445 mg、収率90%、 $M+1=496.2$ 。

[参考例2-8]

4-〔（アミノチオキソメチル）アミノ〕メチル〕ピペリジンカルボン酸tert-ブチルエステルの合成

（〔フルオレン-9-イルメトキシ〕カルボニルアミノ〕チオキソメチル）アミノ〕メチル〕ピペリジンカルボン酸tert-ブチルエステル（2000 mg、4.04 mmol）をDMF（20 mL）に溶解

し、ピペリジン (7.99 ml, 80.8 mmol) を加えて、室温で終夜撹拌した。反応終了後、水 (100 ml) を加えて、酢酸エチル (100 ml × 3 回) で抽出した。抽出した有機層を水 (300 ml × 2 回)、飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、ろ別し濃縮した。シリカゲルカラムクロマトグラフィー (ヘキサン/酢酸エチル = 1/1 → 酢酸エチル) により精製し、4- { [ (アミノチオキソメチル) アミノ] メチル } ピペリジンカルボン酸 tert-ブチルエステルを得た。LC-MS 測定により同定した。

収量 1075 mg、収率 98%、 $M+1 = 274.1$ 。

[参考例 2-9]

4- { [ (イミノメチルチオメチル) アミノ] メチル } ピペリジンカルボン酸 tert-ブチルエステルヨウ化水素塩の合成

4- { [ (アミノチオキソメチル) アミノ] メチル } ピペリジンカルボン酸 tert-ブチルエステル (1075 mg, 3.94 mmol) をテトラヒドロフラン (30 ml) に溶解し、ヨウ化メチル (61.6 mg, 4.33 mmol) を加えて、室温で終夜撹拌した。反応終了後、濃縮し、デシケーター中で減圧乾燥し、4- { [ (イミノメチルチオメチル) アミノ] メチル } ピペリジンカルボン酸 tert-ブチルエステルヨウ化水素塩を得た。LC-MS 測定により同定した。

収量 1597 mg、収率 98%、 $M+1 = 288.1$ 。

[参考例 2-10]

4- { [ (4-オキソヒドロキナゾリン-2-イル) アミノ] メチル } ピペリジンカルボン酸 tert-ブチルエステルの合成

4- { [ (イミノメチルチオメチル) アミノ] メチル } ピペリジンカルボン酸 tert-ブチルエステルヨウ化水素塩 (1722 mg, 4.15 mmol) を DMF (20 ml) に溶解し、トリエチルアミン (0

868 ml、6.23 mmol) とイサト酸無水物 (2029 mg、12.45 mmol) を加えて、80℃で2時間攪拌した。2N水酸化ナトリウム水溶液 (10 ml) を加えて反応を停止した。水 (100 ml) を加え、酢酸エチル (100 ml × 3回) で抽出した。抽出した有機層を水 (100 ml × 2回)、続いて飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、ろ別し濃縮した。シリカゲルカラムクロマトグラフィー (ヘキサン/酢酸エチル = 1/1 → 1/2) により精製し、4- { [(4-オキソヒドロキナゾリン-2-イル) アミノ] メチル } ピペリジンカルボン酸 tert-ブチルエステルを得た。LC-MS測定により同定した。

収量 685 mg、収率 46%、 $M+1 = 359.1$ 。

#### [参考例 2-11]

2- [(4-ピペリジルメチル) アミノ] ヒドロキナゾリン-4-オン塩酸塩の合成

4- { [(4-オキソヒドロキナゾリン-2-イル) アミノ] メチル } ピペリジンカルボン酸 tert-ブチルエステル (685 mg、1.91 mmol) をメタノール (5 ml) に溶解し、4N-塩酸ジオキサン溶液 (5 ml) に加えて、室温で終夜攪拌した。反応終了後、濃縮し、デシケーター中で減圧乾燥し、2- [(4-ピペリジルメチル) アミノ] ヒドロキナゾリン-4-オン塩酸塩を得た。LC-MS測定により同定した。

収量 581 mg、収率定量的、 $M+1 = 259.1$ 。

2- [(4-ピペリジルメチル) アミノ] ヒドロキナゾリン-4-オンの合成

#### [参考例 2-12]

(1-ベンジル-4-ピペリジル) メチルアミンの合成

4-アミノメチルピペリジン (5.754 ml, 50 mmol) をアセトニトリル (200 ml) に溶解し、炭酸カリウム (13.82 g, 100 mmol) とベンジルクロリド (17.13 g, 150 mmol) を加えて、60℃で終夜攪拌した。反応終了後、ろ別を行い、溶媒を留去した。展開溶媒 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NEt<sub>3</sub> = 90/5/5) を用いて、シリカゲルカラムクロマトグラフィーにより精製し、(1-ベンジル-4-ピペリジル) メチルアミンを得た。LC-MS測定により同定した。

収率 91%、収量 9.277 g、M+1 = 205.2。

[参考例 2-13]

2-({[1-ベンジル-4-ピペリジル] メチル} アミノ) ヒドロキナゾリン-4-オンの合成

(1-ベンジル-4-ピペリジル) メチルアミンを、参考例 2-7 (収率 84%)、2-8 (収率 73%)、2-9 (収率定量的)、及び 2-10 (収率 73%) に従い、2-({[1-ベンジル-4-ピペリジル] メチル} アミノ) ヒドロキナゾリン-4-オンを合成した。

[参考例 2-14]

2-[(4-ピペリジルメチル) アミノ] ヒドロキナゾリン-4-オンの合成

2-({[1-ベンジル-4-ピペリジル] メチル} アミノ) ヒドロキナゾリン-4-オン (880 mg, 2.53 mmol) をメタノール (80 mL) に溶解し、窒素置換した。これに水酸化パラジウム (100 mg) を加え、水素雰囲気下、60℃で4時間攪拌した。反応液を室温に冷却して窒素置換し、セライトを通じて濾過した。濾液を減圧濃縮して、2-[(4-ピペリジルメチル) アミノ] ヒドロキナゾリン-4-オンを得た。LC-MSにより同定した。

収量 588 mg, 収率 86%,  $M+1=259.1$ 。

[実施例 2-5]

2-[(1-[(2-クロロフェニル)メチル]-4-ピペリジル)メチル)アミノ]ヒドロキナゾリン-4-オンの合成

2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩 (0.1 mmol, 33 mg, 参考例 2-11) 又は 2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン (0.1 mmol) を DMF/酢酸 (10/1, 1 ml) に溶解し、2-クロロベンズアルデヒド (0.3 mmol, 0.034 ml) と  $\text{NaBH}(\text{OAc})_3$  (0.3 mmol, 64 mg) を加えて、室温で終夜攪拌した。MeOH 1 ml を加えて反応を停止した。反応溶液を SCX (ボンドエルト SCX 500 MG) に注入した。 $\text{CHCl}_3/\text{MeOH}$  (= 1/1, 5 ml  $\times$  2 回) で洗浄した後、2N- $\text{NH}_3/\text{MeOH}$  溶液 5 ml で溶離した。遠心濃縮器を用いて溶媒を留去し、2-[(1-[(2-クロロフェニル)メチル]-4-ピペリジル)メチル)アミノ]ヒドロキナゾリン-4-オンを得た。

収量 15 mg, 収率 39%, 純度 92~96%  $M+1=383.1$ 。

[実施例 2-6~2-30、実施例 2-186~2-200]

化合物番号 2-6~2-30、化合物番号 2-186~2-200 の化合物は、それぞれ対応する反応物を用いて、実施例 2-5 の方法に従い、合成した。結果を表 15 に示す。

[2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩類縁体の合成]

[参考例 2-15]

2-アミノ-5-(メトキシカルボニル)安息香酸の合成

2-アミノ-5-ヨード安息香酸 (4 mmol, 1052 mg) を DMF (10 mL) と MeOH (5 mL) に溶解し、NEt<sub>3</sub> (3 eq, 1.67 mL) を加えた。続いて、酢酸パラジウム (0.1 eq, 90 mg)、dppp (0.1 eq, 165 mg) を加えて、一酸化炭素に置換し、80℃で5時間攪拌した。反応終了後、酢酸 (2.5 mL) を加えて反応を停止した。水 (50 mL) を加えて、酢酸エチル (50 mL × 3回) で抽出した。有機層を、水 (100 mL × 2回) で洗浄後、硫酸ナトリウムで乾燥した。濃縮後、展開溶媒 (Hex/AcOEt = 4/1 → 1/1) を用いて、シリカゲルクロマトグラフィーにより精製し、2-アミノ-5-(メトキシカルボニル)安息香酸を得た。LC-MS測定により同定した。

収率 79%、収量 618 mg、M+1 = 196.0。

#### 《置換イサト酸無水物の合成 その1》

##### [参考例 2-16]

#### 2-(Boc)アミノ-6-クロロ安息香酸の合成

2-アミノ-6-クロロ安息香酸 (1.13 g, 6.59 mmol) をテトラヒドロフラン (5.0 mL) に溶解し、ナトリウムビストリメチルシリルアミド / 1.0 M in THF (19.8 mL, 19.8 mmol) を滴下した。これを15分間攪拌した後に、(Boc)<sub>2</sub>O (1.82 mL, 7.91 mmol) のテトラヒドロフラン溶液 (2.0 mL) を滴下し、3時間攪拌した。反応液に水 (20 mL) 及び1規定塩酸 (約 25 mL) を加えて、pH 約 4 に調製した。これを酢酸エチル (40 mL × 3回) で抽出し、得られた有機層を水 (50 mL × 2回)、飽和食塩水 (50 mL) で洗浄し、無水硫酸マグネシウムで乾燥させた。これを減圧濃縮して得られた濃縮残渣を、シリカゲルカラムクロマトグラフィー (塩化メチレン：メタノール：酢酸 = 95 : 5 : 1) で

精製して、2-(Boc)アミノ-6-クロロ安息香酸を得た。LC-MSとNMRにより同定した。

収量1.62 g, 収率90%,  $M+23=294.0$ 。

$^1\text{H-NMR}$  (270 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.40 (1H, s), 8.04 (1H, d,  $J=8.2$  Hz), 7.35 (1H, t,  $J=8.2$  Hz), 7.13 (1H, d,  $J=8.2$  Hz), 1.52 (9H, s) ppm.

以下の中間体を、それぞれ対応する反応物を用いて、参考例2-16の方法に従い合成した。

2-(Boc)アミノ-3-クロロ安息香酸: 収量3.58 g, 収率70%,  $M+23=294.0$ 。

2-(Boc)アミノ-5-メトキシカルボニル安息香酸: 収量988 mg, 収率49%,  $M+1=296.1$ 。

#### [参考例2-17]

##### 5-クロロイサト酸無水物の合成

2-(Boc)アミノ-6-クロロ安息香酸 (1.51 g, 5.56 mmol) を、トルエン (20 mL) に懸濁し、加熱還流させた。ここに、オキザリルクロリド (0.572 mL, 6.67 mmol) を滴下し、10分間激しく攪拌した。反応液を氷冷した後に、析出した結晶を濾取して、*n*-ヘキサンで洗浄し、デシケーター中で乾燥し、5-クロロイサト酸無水物を得た。

収量769 mg, 収率70%,  $M+1=198.0$ 。

$^1\text{H-NMR}$  (270 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  11.8 (1H, s), 7.65 (1H, t,  $J=8.2$  Hz), 7.30 (1H, d,  $J=8.2$  Hz), 7.10 (1H, d,  $J=8.2$  Hz) ppm.

以下の中間体をそれぞれ対応する反応物を用いて、参考例2-17の

方法に従い合成した。

8-クロロイサト酸無水物：収量 1.42 g, 収率 55%,  $M+1=197.9$

6-メトキシカルボニルイサト酸無水物：収量 397 mg, 収率 57%,  $M+1=222.0$ 。

6-トリフルオロメチルイサト酸無水物：収量 1.52 g, 収率 50%,  $M+1=232.0$ 。

#### 《置換イサト酸無水物の合成 その2》

##### [参考例 2-18]

6-(トリフルオロメトキシ)イサト酸無水物の合成

5-(トリフルオロメトキシ)アントラニル酸 (2.221 g, 10.04 mmol) を THF (25 mL) に溶解し、トリホスゲン (1.08 g) を加えて、室温で終夜攪拌した。反応終了後、溶媒を除去し、残渣を減圧乾燥した。アセトン及びヘキサンで洗浄し、デシケーター中で減圧乾燥し、6-(トリフルオロメトキシ)イサト酸無水物を得た。LC-MSにより同定した。

収量 1.516 g, 収率 61%,  $M+1=248.0$ 。

以下の中間体をそれぞれ対応する反応物を用いて、参考例 2-18の方法に従い合成した。

6-ニトロイサト酸無水物：収量 0.889 g, 収率 43%,  $M+1=208.9$ 。

6-メチルイサト酸無水物：収量 1.251 g, 収率 70%,  $M+1=178.0$ 。

5-カルボキシルイサト酸無水物：収量 1.352 g, 収率 65%,  $M+1=208.0$ 。

6-フルオロイサト酸無水物： $M+1=182.0$ 。



6-ヒドロキシイサト酸無水物： $M+1=180.0$ 。

6-メトキシイサト酸無水物： $M+1=194.0$ 。

5-メチルイサト酸無水物： $M+1=178.0$ 。

6-アセトアミドイサト酸無水物：収量0.4g、収率9%、 $^1\text{H-NMR}$  (200MHz, DMSO)： $\delta$  2.05 (s, 3H), 7.05 (d, 1H), 7.85 (dd, 1H), 8.25 (d, 1H), 10.15 (s, 1H)。

#### 《置換イサト酸無水物の合成 その3》

##### [参考例2-19]

N-(3, 4-ジメチルフェニル)-2-ヒドロキシミノ-アセトアミドの合成

クロラール (73.8g, 0.41mol)、硫酸ナトリウム (1066g) の水 (2.5ml) 溶液、3, 4-ジメチルアミン (50g, 0.41mol) 及び濃塩酸 (35.4ml) の水溶液 (600ml) の混合溶液にヒドロキシルアミン (90g, 0.41mmol) の水溶液 (500ml) を添加し、過熱還流下1時間攪拌する。得られた熱溶液を濾過し、得られた沈殿を水及びジクロロメタンにて洗浄し、N-(3, 4-ジメチルフェニル)-2-ヒドロキシミノ-アセトアミドを得た。

収量63g、収率80%

##### [参考例2-20]

4, 5-ジメチル-1H-インドール-2, 3-ジオンの合成

濃硫酸 (85ml) の水溶液 (17ml) に、N-(3, 4-ジメチルフェニル)-2-ヒドロキシミノ-アセトアミド (30g, 0.156mmol) をゆっくり添加し、85℃にて2時間攪拌する。得られた溶液を氷冷水に注ぎ、析出した橙色固体を濾取する。得られた固体を

10%水酸化ナトリウム水溶液に溶解させ、活性炭を添加し攪拌する。得られた溶液を濾過し酢酸を用いて酸性にして4, 5-ジメチル-1H-インドール-2, 3-ジオンを結晶として得た。

収量9.8g、収率30%

$^1\text{H-NMR}$  (200MHz, DMSO-d<sub>6</sub>) : 2.25 (s, 3H), 2.55 (s, 3H), 6.95 (d, 2H), 7.50 (d, 2H), 10.55 (bs, 1H)

[参考例2-21]

6-アミノ-2, 3-ジメチル安息香酸の合成

4, 5-ジメチル-1H-インドール-2, 3-ジオン (9.8g、0.056mmol) 及び水酸化ナトリウム (8.1g、0.2mol) の水 (80ml) 溶液を85℃に加熱し、10%過酸化水素水溶液 (43ml) をゆっくり加える。得られた溶液を85℃にて2時間攪拌した後、室温まで冷却し、濾過する。濾液に硫酸を用いて酸性にして6-アミノ-2, 3-ジメチル安息香酸を結晶として得た。

収量3.6g、収率38%

$^1\text{H-NMR}$  (200MHz, DMSO-d<sub>6</sub>) : 2.05 (s, 3H), 2.15 (s, 3H), 6.50 (d, 2H), 6.92 (d, 2H)

[参考例2-22]

5, 6-ジメチルイサト酸無水物の合成

6-アミノ-2, 3-ジメチル安息香酸 (1g、6mmol) を用いて参考例2-18の方法に従い、5, 6-ジメチルイサト酸無水物を合成した。

収量500mg、収率92%

$^1\text{H-NMR}$  (200, DMSO) : 2.25 (s, 3H), 2.55

(s, 3H), 6.92 (d, 2H), 7.50 (d, 2H), 10.65 (bs, 1H)

以下のイサト酸無水物をそれぞれ対応する反応物を用いて、参考例 2-19~22の方法に従い合成した。

5-メチル-6-フルオロ-イサト酸無水物:

$^1\text{H-NMR}$  (200 MHz, DMSO-d<sub>6</sub>): 2.45 (s, 3H), 6.75 (dd, 1H), 7.45 (dd, 1H), 11.0 (bs, 1H).

5-メチル-6-ブロモ-イサト酸無水物:

$^1\text{H-NMR}$  (200, DMSO): 2.75 (s, 3H), 6.85 (d, 1H), 7.95 (d, 1H), 10.75 (bs, 1H)

6-(N,N-ジメチルアミノ-スルホニル)-イサト酸無水物:

$^1\text{H-NMR}$  (200 MHz, DMSO-d<sub>6</sub>): 2.65 (s, 6H), 7.35 (d, 1H), 8.05 (s, 1H), 8.15 (d, 1H), 11.2 (bs, 1H)

6-メトキシ-7-メチル-イサト酸無水物:

$M+1=208.0$

5-メチル-6-メトキシ-イサト酸無水物:

$M+1=208.0$

6,7-ジメチル-イサト酸無水物:

$^1\text{H-NMR}$  (200, DMSO): 2.24 (s, 3H), 2.29 (s, 3H), 6.91 (s, 1H), 7.66 (s, 1H), 10.60 (bs, 1H).

5,7-ジメチル-イサト酸無水物:

$^1\text{H-NMR}$  (200 MHz, DMSO-d<sub>6</sub>): 6.91 (s, 1H); 6.79 (s, 1H); 2.56 (s, 3H); 2.32 (s,

3 H)

6-エチル-イサト酸無水物:

$^1\text{H-NMR}$  (200, DMSO): 7.73 (s, 1H); 7.65 (d, 1H); 7.09 (d, 1H); 2.64 (q, 2H); 1.18 (t, 3H).

6-エトキシ-イサト酸無水物:

$^1\text{H-NMR}$  (200 MHz, DMSO-d<sub>6</sub>): 1.35 (t, 3H), 4.05 (q, 2H), 7.05 (d, 1H), 7.35 (d, 1H), 7.45 (dd, 1H), 10.5 (bs, 1H)

5-メチル-8-フルオロ-イサト酸無水物:

$^1\text{H-NMR}$  (200 MHz, DMSO-d<sub>6</sub>): 2.56 (s, 3H), 7.05 (dd, 1H), 7.55 (dd, 1H)

5、8-ジメチル-イサト酸無水物:

$^1\text{H-NMR}$  (200 MHz, DMSO-d<sub>6</sub>): 2.27 (s, 3H), 2.56 (s, 3H), 7.00 (d, 1H), 7.45 (d, 1H)

6-イソプロピル-イサト酸無水物:

$^1\text{H-NMR}$  (200, DMSO): 7.73 (s, 1H); 7.65 (d, 1H); 7.10 (d, 1H); 2.95 (h, 1H); 1.20 (d, 6H).

6-スルフォニルフェニル-イサト酸無水物:

$^1\text{H-NMR}$  (200 MHz, DMSO-d<sub>6</sub>): 7.35 (d, 1H), 7.65 (m, 3H); 8.00 (m, 2H); 8.25 (dd, 1H), 8.35 (d, 1H), 11.30 (s, 1H)

《置換イサト酸無水物の合成 その4》

[参考例2-23]

## 2-アミノ-5-メチルスルファニル安息香酸の合成

5-クロロ-2-ニトロ安息香酸 (50 g、0.25 mmol) の水溶液 (500 ml) に4規定水酸化ナトリウム水溶液 (42 ml) を添加する。得られた溶液に  $\text{Na}_2\text{S}$  (66 g、0.8 mmol) の水溶液 (150 ml) を加え、55℃にて2.5時間攪拌する。得られた溶液に20%水酸化ナトリウム水溶液 (50 ml) 及びジメチル硫酸 (63 ml、0.66 mmol) を加え、80℃にて1時間攪拌する。得られた溶液に塩酸を加え、析出した沈殿を濾取、エーテルにて洗浄し、2-アミノ-5-メチルスルファニル安息香酸を得た。

収量 14 g、収率 26 %

[参考例 2-24]

## 2-アミノ-5-メチルスルホニル安息香酸の合成

2-アミノ-5-メチルスルファニル安息香酸 (12 g、0.055 mmol) のジクロロメタン及びアセトン溶液に、m-クロロ-過安息香酸 (42.7 g、0.165 mmol) を添加し、室温にて3時間攪拌した。析出した固体を濾取、エーテル及びジクロロメタンにて洗浄し、2-アミノ-5-メチルスルホニル安息香酸を得た。

収量 4 g、収率 30 %

$^1\text{H-NMR}$  (200 MHz,  $\text{DMSO-d}_6$ ) : 3.15 (s, 3H), 6.95 (dd, 1H), 7.55 (bs, 2H), 7.77 (dd, 1H), 8.25 (d, 1H).

[参考例 2-25]

## 6-メタンスルホニル-イサト酸無水物の合成

2-アミノ-5-メチルスルホニル安息香酸 (2 g、9.6 mmol) を用いて、参考例 11 の方法に従い、6-メタンスルホニル-イサト酸無水物を合成した。

収量 1500 mg、収率 66%

$^1\text{H-NMR}$  (200 MHz, DMSO- $d_6$ ) : 3.35 (s, 3H), 7.35 (d, 1H), 8.25 (dd, 1H), 8.35 (d, 1H), 9.90 (s, 1H)

[参考例 2-26]

2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩類縁体の合成

参考例 2-17 又は 2-18 を用いて合成したイサト酸無水物に対して、参考例 2-10 及び参考例 2-11 に従って、以下に示す中間体を合成した。

5-クロロ-2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩。

8-クロロ-2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩。

6-メトキシカルボニル-2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩。

6-トリフルオロメチル-2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩。

6-トリフルオロメトキシ-2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩。

6-ニトロ-2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩。

6-メチル-2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩。

5-メトキシカルボニル-2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩。

6-フルオロ-2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩。

6-ヒドロキシ-2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩。

6-メトキシ-2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩。

5-メチル-2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩。

[実施例 2-201~2-250、499、511、513、565]

化合物番号 2-201~2-250、499、511、513、及び 565 の化合物を、参考例 2-15~2-19 によって合成した、それぞれ対応する 2-[(4-ピペリジルメチル)アミノ]ヒドロキナゾリン-4-オン塩酸塩類縁体と反応物を用いて、実施例 2-5 の方法に従い、合成した。結果を表 15 に示す。

### 3-Nアルキルキナゾリノン誘導体の合成法

[参考例 2-27]

4-( {[ (メチルアミノ) チオキソメチル] アミノ } メチル) ピペリジンカルボン酸 *tert* ブチルエステルの合成

1-Boc-4-アミノメチルピペリジン (642 mg、3 mmol) を THF (8 ml) に溶解し、メチルイソチオシアネート (241 mg、3.3 mmol) を加えて、終夜室温で攪拌した。反応終了後、シリカゲルカラムクロマトグラフィー (Hex/AcOEt = 1/4) により精製し、4-( {[ (メチルアミノ) チオキソメチル] アミノ } メチル) ピペリジンカルボン酸 *tert* ブチルエステルを得た。LC-MS 測定により同定した。

収量 839 mg、収率 98%、 $M+1=288.1$ 。

[参考例 2-28]

3-メチル-2-[(4-ピペリジルメチル)アミノ]-3-ヒドロキナゾリン-4-オン塩酸塩の合成

参考例 2-9 (収率 94%、収量 1171 mg)、参考例 2-10 (収率 33%、収量 331 mg)、参考例 2-11 (収率定量的、収量 116 mg) に従い、3-メチル-2-[(4-ピペリジルメチル)アミノ]-3-ヒドロキナゾリン-4-オン塩酸塩を合成した。

収率定量的、収量 116 mg、 $M+1=273.1$ 。

[実施例 2-492~2-495]

化合物番号 2-492~2-495 の化合物を、参考例 2-20、2-21 によって合成した化合物に対し、それぞれ対応する反応物を用いて、実施例 2-5 の方法に従い合成した。結果を表 15 に示す。

表 15

化合物 No.2-	収量(mg)	収率(%)	MW	M+1
1	27.0	44	416.1	417.1
2	25.0	38	450.1	453.2 (Cl×3)
3	4.1	6	432.2	433.2
4	159.0	10	398.2	399.3
5	15.0	39	382.1	383.1
6	21.0	55	382.1	383.1
7	25.0	65	382.1	383.1
8	23.3	92	378.2	379.1
9	36.0	100	378.2	379.1
10	22.6	97	376.2	377.2
11	23.2	97	398.2	399.1
12	25.3	95	442.1	443.0
13	27.7	100	456.1	458.1 (Br)
14	19.3	72	444.1	445.0



15	24.8	97	426.1	427.1
16	23.3	90	432.1	433.1
17	23.3	97	400.1	401.1
18	24.3	90	401.2	402.2
19	29.1	100	404.2	405.2
20	11.9	50	394.2	395.2
21	13.1	55	393.2	394.2
22	12.1	53	378.2	379.2
23	17.0	71	398.2	399.2
24	12.5	60	348.2	349.2
25	7.6	35	362.2	363.2
26	1.6	3	476.0	479.0 (Br)
27	6.0	15	389.2	390.2
28	12.0	30	466.1	467.2
29	12.0	28	466.1	467.1
30	14.0	40	398.2	399.1
186	15.0	57	432.1	433.0
187	25.8	95	443.1	444.1
188	25.0	96	428.2	429.1
189	21.6	85	416.1	417.1
190	22.6	80	460.1	463.0 (Br,Cl)
191	24.4	93	427.1	428.1
192	26.6	96	412.2	413.1
193	21.3	75	466.1	467.1
194	17.2	65	435.2	436.2
195	24.2	90	438.1	439.1
196	21.4	92	382.2	383.1
197	22.5	90	410.2	411.1
198	16.5	57	476.1	479 (Br,Cl)
199	7.8	30	432.2	433.1
200	6.3	26	396.2	397.1
201	1.0	5	466.1	469.1 (Cl × 3)

202	4.7	34	462.1	463.0
203	4.0	21	490.1	491.1
204	4.8	34	466.1	469.0 (CI × 3)
205	2.0	41	490.1	491.0
206	2.5	14	466.1	467.0
207	2.8	14	516.1	517.1
208	2.9	15	490.1	491.1
209	3.9	19	500.1	501.1
210	2.4	12	446.1	447.1
211	5.0	26	450.1	451.1
212	2.5	13	448.1	449.0
213	4.0	9	477.1	478.0
214	20.0	37	468.1	469.1
215	7.0	13	450.1	451.0
216	2.8	6	446.1	447.1
217	3.0	8	457.1	458.1
218	2.2	13	432.1	433.0
219	9.5	74	428.2	429.3
220	5.5	31	456.2	457.1
221	5.2	40	432.1	433.1
222	3.1	68	456.2	457.2
223	6.7	40	432.1	433.1
224	5.0	27	482.1	483.1
225	3.5	20	456.2	457.2
226	3.4	18	466.1	467.1
227	3.0	17	412.2	413.1
228	5.9	33	416.1	417.0
229	4.0	23	432.2	433.1
230	2.0	23	428.2	429.2
231	1.0	6	456.2	457.2
232	1.6	9	432.2	433.2
233	1.7	9	456.2	457.3

234	7.2	43	432.2	433.1
235	8.5	46	482.2	483.1
236	2.6	15	456.2	457.2
237	2.0	11	466.2	467.2
238	3.7	21	412.2	413.2
239	5.3	30	416.2	417.1
240	6.3	38	410.2	411.2
241	2.9	36	406.2	407.3
242	9.2	55	434.2	435.2
243	10.2	62	410.2	411.2
244	21.1	121	434.2	435.2
245	10.0	63	410.2	411.1
246	15.7	89	460.2	461.2
247	2.1	13	434.2	435.2
248	5.8	33	444.2	445.2
249	4.4	26	390.2	391.2
250	7.6	45	394.2	395.1
492	5.0	17	446.1	447.1
493	9.0	31	412.2	413.2
494	16.0	55	412.2	413.2
495	15.0	52	390.2	391.2
499	12.0	38	430.9	431.1
511	10.0	32	434.9	435.1
513	6.0	16	430.9	431.1
565	9.2	26	442.9	443.1

### ベンゾチアジアジン誘導体の合成法

#### [参考例 3 - 1]

7-フルオロ-2H, 4H-ベンゾ[e]1, 2, 4-チアジアジン-1, 1, 3-トリオンの合成

クロロスルホニルイソシアナート (3.29 mL, 37.8 mmol)

）をニトロエタン（45 mL）に溶解し、 $-80^{\circ}\text{C}$ に冷却した。これに、4-フルオロアニリン（3.50 g, 31.5 mmol）のニトロメタン溶液（5 mL）を、10分間で滴下した。反応液を $0^{\circ}\text{C}$ まで昇温し、塩化アルミニウム（5.33 g, 40.0 mmol）を加えた。30分間加熱還流した後、室温まで冷却してから、反応液を氷水（120 mL）に注いだ。析出した結晶を濾取、乾燥して、7-フルオロ-2H, 4H-ベンゾ[e]1, 2, 4-チアジアジン-1, 1, 3-トリオンを得た。

収量 3.72 g、収率 55%、 $M+1=217.0$ 。

参考例 3-1 に従い、7-メチル-2H, 4H-ベンゾ[e]1, 2, 4-チアジアジン-1, 1, 3-トリオン（4.24 g、67%）、7-エチル-2H, 4H-ベンゾ[e]1, 2, 4-チアジアジン-1, 1, 3-トリオン（2.6 g、37%）、及び7-メトキシ-2H, 4H-ベンゾ[e]1, 2, 4-チアジアジン-1, 1, 3-トリオン（1.09 g、16%）を合成した。

#### [参考例 3-2]

##### 2-アミノ-5-フルオロベンゼンスルホンアミドの合成

7-フルオロ-2H, 4H-ベンゾ[e]1, 2, 4-チアジアジン-1, 1, 3-トリオン（3.00 g, 13.9 mmol）を、50%硫酸（90 mL）に懸濁し、 $130^{\circ}\text{C}$ で1時間攪拌した。反応液を氷浴で冷却しながら、40%水酸化ナトリウム水溶液を加えて中和した。この水溶液を200 mLまで減圧濃縮し、析出物を濾取した。これを酢酸エチル（100 mL）に懸濁させて、不溶物を濾別した。濾液を減圧濃縮、乾燥して2-アミノ-5-フルオロベンゼンスルホンアミドを得た。

収量 2.27 g、収率 86%、 $M+1=191.0$ 。

参考例 3-2 に従い、2-アミノ-5-メチルベンゼンスルホンアミド（収量 958 mg、収率 55%）、2-アミノ-5-エチルベンゼンスルホンアミド（収量 1.4 g、収率 64%）、及び 2-アミノ-5-メトキシベンゼンスルホンアミド（収量 696 mg、収率 72%）を合成した。

[参考例 3-3]

2-ブロモ-4, 5-ジメチルニトロベンゼンの合成

磁気攪拌子を備えた 300 mL なすフラスコに、4, 5-ジメチル-2-ニトロアニリン 10.02 g (60.3 mmol) を量り取り、48% 臭化水素酸水溶液 30 mL と水 30 mL を加えて激しく攪拌した。懸濁液は、橙色となった。橙色サスペンションのまま、氷水-食塩浴上で冷却し、液温が 5℃ を上回らないように亜硝酸ナトリウム 4.422 g (64.1 mmol) を 24 mL の水に溶解した水溶液を、橙色サスペンションに滴下した。滴下が完了したとき、反応液は茶褐色溶液になった。氷水浴上でそのまま茶褐色溶液を攪拌した。

磁気攪拌子を備えた 1 L 三角フラスコへ、48% 臭化水素酸水溶液 30 mL、臭化銅 (I) 11.85 g (82.6 mmol) を入れて氷水浴上で冷却し、攪拌しながら、上で得られた茶褐色溶液を 5 分間かけて滴下した。滴下終了後、氷水浴上で 20 分間攪拌した後、80℃ の油浴上で激しく攪拌しながら加熱した。

1 時間後に加熱を止め、室温で終夜攪拌した反応混合物を、酢酸エチル 300 mL × 2 回で抽出し、有機層を合わせて 5 規定塩酸、飽和重曹水、飽和食塩水の順で洗浄した。有機層を無水硫酸ナトリウム上で乾燥させた後、乾燥剤を減圧濾過により除去して濾液を濃縮し、黄褐色固体を得た。この黄褐色固体をシリカゲルカラムクロマトグラフィー (Hex : EtOAc = 10 : 1) で精製し、茶褐色針状晶を得た。この茶

褐色針状晶をヘキサンから再結晶し、黄色針状晶として2-ブロモ-4,5-ジメチルニトロベンゼンを得ることができた。

収量6.637 g, 収率47.9%

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ )

$\delta$  2.29 (3H, s), 2.31 (3H, s), 7.49 (1H, s), 7.69 (1H, s)

[参考例3-4]

2-ブロモ-4,5-ジメチルアニリンの合成

磁気攪拌子を備えた100 mLなすフラスコに2-ブロモ-4,5-ジメチルニトロベンゼン1.006 g (4.375 mmol)を量り取り、2-メトキシエタノール10 mLと水10 mLを加えて攪拌し、懸濁させた。ここへハイドロサルファイトナトリウム2.799 g (10.07 mmol)を加えて100℃の油浴上で激しく攪拌しながら加熱した。2.5時間後、得られた薄黄色サスペンションを加熱攪拌したまま水10 mLを加えると不溶物が消失し、薄黄色溶液となった。この薄黄色溶液に、濃塩酸10 mLを5分間かけて滴下し、滴下後20分間還流させた。

つづいて室温まで反応液の温度を下げ、炭酸ナトリウムを粉末で加えて反応液を中和すると、pH 7~8付近で薄茶色~白色の沈殿物が析出した。集めた沈殿物を乾燥させ白色固体として2-ブロモ-4,5-ジメチルアニリンを得た。

収量0.832 g, 収率95.0%。

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ )

$\delta$  2.13 (6H, s), 6.59 (1H, s), 7.16 (1H, s)

[参考例3-5]

5-ブロモ-7, 8-ジメチル-2H, 4H-ベンゾ[e]1, 2, 4-チアジアジン-1, 1, 3-トリオンの合成

参考例3-1に従い、表題化合物を得た。

収量5.27g、収率83%、 $M+1=304.9$ 。

$^1\text{H-NMR}$  (270MHz,  $\text{CD}_3\text{OD}$ )

$\delta$  7.69 (1H, s), 2.55 (3H, s), 2.31 (3H, s)

[参考例3-6]

7, 8-ジメチル-2H, 4H-ベンゾ[e]1, 2, 4-チアジアジン-1, 1, 3-トリオンの合成

5-ブロモ-7, 8-ジメチル-2H, 4H-ベンゾ[e]1, 2, 4-チアジアジン-1, 1, 3-トリオン (5.27g, 17.3mmol) をメタノール (60mL) に懸濁し、ギ酸アンモニウム (5.45g, 86.5mmol, 5eq) を加えて窒素置換した。これに10%パラジウム-カーボン粉末 (1.84g, 1.73mmol, 10mol%) を加えて、4時間加熱還流した。反応液を室温まで冷却し、セライトを通じて濾過した。濾液を氷冷して、析出した結晶を濾取、乾燥して、7, 8-ジメチル-2H, 4H-ベンゾ[e]1, 2, 4-チアジアジン-1, 1, 3-トリオンを得た。

収量3.66g、収率94%、 $M+1=227.0$ 。

$^1\text{H-NMR}$  (270MHz,  $\text{CD}_3\text{OD}$ )

$\delta$  7.19 (1H, d,  $J=8.3\text{Hz}$ ), 6.78 (1H, d,  $J=8.3\text{Hz}$ ), 2.57 (3H, s), 2.26 (3H, s)

[参考例3-7]

2-アミノ-5, 6-ジメチルベンゼンスルホンアミドの合成

参考例3-2に従い、表題化合物を得た。

収量 1.98 g、収率 61%、 $M+1=201.1$ 。

$^1\text{H-NMR}$  (270 MHz, DMSO- $d_6$ )

$\delta$  7.20 (2H, s), 6.98 (1H, d,  $J=8.4$  Hz), 6.55 (1H, d,  $J=8.4$  Hz), 5.98 (2H, s), 2.39 (3H, s), 2.10 (3H, s)

参考例 3-3~3-7 に従い、4-メチル-2-ニトロアニリンを原料にして、2-アミノ-6-メチルベンゼンスルホンアミドを合成した。収量 555 mg、収率 45%。

$^1\text{H-NMR}$  (270 MHz, DMSO)

$\delta$  2.48 (3H, s), 6.12 (2H, s), 6.40 (1H, d,  $J=7.0$  Hz), 6.62 (1H, d,  $J=8.1$  Hz), 6.99-7.04 (1H, dd,  $J=8.1$  Hz,  $J=7.0$  Hz), 7.19 (2H, s)

[参考例 3-8]

4- { [ (7-フルオロ-1,1-ジオキソ-4H-ベンゾ [e] 1,2,4-チアジアジン-3-イル) アミノ] メチル } ピペリジンカルボン酸 *tert* ブチルエステルの合成

1-N-Boc-4-アミノメチルピペリジン (1.08 g, 5.04 mmol) をアセトニトリル (8.0 mL) に溶解し、0℃に冷却した。これに 1,1'-チオカルボニルジイミダゾール (988 mg, 5.54 mmol) 及びイミダゾール (103 mg, 1.51 mmol) のアセトニトリル溶液 (10 mL) を滴下して、室温で2時間攪拌した。反応液に 2-アミノ-5-フルオロベンゼンスルホンアミド (1.25 g, 6.55 mmol) 及びジメチルアミノピリジン (739 mg, 6.05 mmol) を加え、80℃で1晩攪拌した。これにジイソプロピルカルボジイミド (0.233 mL, 1.51 mmol) を加



えて、1時間攪拌した。反応液を室温に冷却した後に減圧濃縮して、残渣を酢酸エチル（50 mL）に溶解した。これを水（20 mL）及び飽和食塩水（20 mL）で洗浄した後に、無水硫酸ナトリウムで乾燥させた。減圧濃縮後の残渣をシリカゲルカラムクロマトグラフィー（n-ヘキサン：酢酸エチル＝3：2→2：3）で精製して、4- { [ (7-フルオロ-1, 1-ジオキソ-4H-ベンゾ [e] 1, 2, 4-チアジアジン-3-イル) アミノ] メチル} ピペリジンカルボン酸 *Tert* ブチルエステルを得た。

収量 1.66 g、収率 80%、 $M-Boc + 2H = 313.1$ 。

参考例 3-8 に従い、

4- { [ (1, 1-ジオキソ-4H-ベンゾ [e] 1, 2, 4-チアジアジン-3-イル) アミノ] メチル} ピペリジンカルボン酸 *tert* ブチルエステル：収量 132 mg、収率 67%

4- { [ (7-メチル-1, 1-ジオキソ-4H-ベンゾ [e] 1, 2, 4-チアジアジン-3-イル) アミノ] メチル} ピペリジンカルボン酸 *tert* ブチルエステル：収量 681 mg、収率 49%

4- { [ (7-メトキシ-1, 1-ジオキソ-4H-ベンゾ [e] 1, 2, 4-チアジアジン-3-イル) アミノ] メチル} ピペリジンカルボン酸 *tert* ブチルエステル：収量 766 mg、収率 63%

4- { [ (7-エチル-1, 1-ジオキソ-4H-ベンゾ [e] 1, 2, 4-チアジアジン-3-イル) アミノ] メチル} ピペリジンカルボン酸 *tert* ブチルエステル：収量 525 mg、収率 36%

4- { [ (8-メチル-1, 1-ジオキソ-4H-ベンゾ [e] 1, 2, 4-チアジアジン-3-イル) アミノ] メチル} ピペリジンカルボン酸 *tert* ブチルエステル：収量 203 mg、収率 44%

4- { [ (7, 8-ジメチル-1, 1-ジオキソ-4H-ベンゾ [e]

1, 2, 4-チアジアジン-3-イル) アミノ] メチル} ピペリジンカルボン酸 *tert* ブチルエステル: 収量 175 mg、収率 30% を合成した。

[参考例 3-9]

7-フルオロ-3-[(4-ピペリジルメチル) アミノ]-4H-ベンゾ[e] 1, 2, 4-チアジアジン-1, 1-ジオン塩酸塩の合成

参考例 2-11 に従い、7-フルオロ-3-[(4-ピペリジルメチル) アミノ]-4H-ベンゾ[e] 1, 2, 4-チアジアジン-1, 1-ジオンを得た。収量 497 mg、収率 90%、 $M+1=313.1$ 。

参考例 3-9 に従い、以下の化合物を合成した。

7-メチル-3-[(4-ピペリジルメチル) アミノ]-4H-ベンゾ[e] 1, 2, 4-チアジアジン-1, 1-ジオン塩酸塩: 収量 691 mg、収率定量的。

3-[(4-ピペリジルメチル) アミノ]-4H-ベンゾ[e] 1, 2, 4-チアジアジン-1, 1-ジオン塩酸塩: 収率定量的、収量 116 mg、 $M+1=295.1$ 。

7-メトキシ-3-[(4-ピペリジルメチル) アミノ]-4H-ベンゾ[e] 1, 2, 4-チアジアジン-1, 1-ジオン塩酸塩: 収量 505 mg、収率 79%、 $M+1=325.0$ 。

7-エチル-3-[(4-ピペリジルメチル) アミノ]-4H-ベンゾ[e] 1, 2, 4-チアジアジン-1, 1-ジオン塩酸塩: 収量 470 mg、収率定量的、 $M+1=323.1$ 。

8-メチル-3-[(4-ピペリジルメチル) アミノ]-4H-ベンゾ[e] 1, 2, 4-チアジアジン-1, 1-ジオン塩酸塩: 収量 97 mg、収率 63%、 $M+1=309.1$ 。

7, 8-ジメチル-3-[(4-ピペリジルメチル) アミノ]-4H-

ベンゾ[e]1,2,4-チアジジン-1,1-ジオン塩酸塩：収量 44 mg、収率 89%、 $M+1=323.1$ 。

[実施例 3-1～3-10、3-208、220、223、235、238、368、504、505、511、523、525～527、555、577]

化合物番号 3-1～3-10 及び 3-208、220、223、235、238、368、504、505、511、523、525～527、555、577 の化合物を、参考例 3-1～3-9 によって合成した化合物に対し、それぞれ対応する反応物を用いて、実施例 2-5 の方法に従い、合成した。結果を表 16 に示す。

表 16

化合物 No.3-	収量(mg)	収率(%)	MW	M+1
1	10.0	35	468.0	469.0
2	7.0	26	434.1	435.1
3	9.0	34	434.1	435.0
4	13.0	52	412.1	413.1
5	25.2	66.2	482.1	483.0
6	20.8	58.9	448.1	449.1
7	25.4	71.9	448.2	449.2
8	9.9	26.1	486.1	487.0
9	20.5	58.1	452.1	453.1
10	38.3	100	452.2	453.1
208	20.4	54	499.4	499.0
220	4.7	11	483.4	483.0
223	28.7	81	465.0	465.1
235	8.1	21	449.0	449.1
238	34.1	97	464.6	465.2
368	4.5	12	463.0	463.1
504	4.0	13	497.4	497.1

505	10.0	35	463.0	463.1
511	9.8	24	467.0	467.0
523	15.0	50	470.9	471.1
525	5.4	13	467.0	467.1
526	8.0	27	481.0	481.1
527	18.0	60	483.0	483.1
555	17.2	37	481.0	481.1
577	9.4	25	479.1	479.0

### ジヒドロキナゾリン誘導体の合成法

#### [参考例 4-1]

4-（ジヒドロキナゾリン-2-アミノメチル）ピペリジン塩酸塩の合成

1-Boc-4-（アミノメチル）ピペリジン（350 mg、1.6 mmol）を $\text{CH}_3\text{CN}$ （15 ml）に溶解し、チオカルボニルジイミダゾール（350 mg、1.9 mmol）を加え、室温で1時間攪拌した。反応液に、2-アミノベンジルアミン（240 mg、1.9 mmol）を加え、室温で1時間攪拌した。溶媒を減圧留去し、1-Boc-4-（2-アミノベンジルチオウレアメチル）ピペリジンを得た。LC-MSにより同定した。

$M+1 = 379.2$ 。

1-Boc-4-（2-アミノベンジルチオウレアメチル）ピペリジンを $\text{EtOH}$ （30 ml）に溶かし、酸化水銀（800 mg）を加え、1時間還流した。溶媒を減圧留去し、1-Boc-4-（ジヒドロキナゾリン-2-アミノメチル）ピペリジンを得た。LC-MSにより同定した。

$M+1 = 345.2$ 。

1-Boc-4-(ジヒドロキナゾリン-2-アミノメチル)ピペリジンをメタノール(10 ml)に溶かし、4規定塩化水素/1, 4-ジオキサン溶液(16 ml)を加え、50℃で90分攪拌した。溶媒を減圧留去し、4-(ジヒドロキナゾリン-2-アミノメチル)ピペリジン塩酸塩を得た。LC-MSにより同定した。

収量 449 mg、89%、 $M+1=245.1$ 。

[実施例 4-1 ~ 4-5]

化合物番号 4-1 ~ 4-5 の化合物を、それぞれ対応する反応物を用いて、実施例 2-5 の方法に従い合成した。結果を表 17 に示す。

[実施例 4-7]

2, 4-ジクロロ-6-[(4-{[(6-クロロ(1, 4-ジヒドロキナゾリン-2-イル))アミノ]メチル}ピペリジル)メチル]フェノールの合成

化合物番号 2-193 (2.5 mg、0.028 mmol) を THF (0.5 mL) に溶解し、1N-BH<sub>3</sub>・THF 溶液 (0.56 ml、0.56 mmol) を加え、80℃にて24時間攪拌した。得られた溶液に、5N-NaOH 水溶液 (0.5 mL) を加え、80℃にて5時間攪拌した。得られた溶液を酢酸エチルにて抽出 (2 mL × 2 回)、Sep-Pak-Dry (商品名、バリアン製、硫酸ナトリウムのカートリッジ) に移して乾燥し、さらに SCX (ボンドエルト SCX 500 MG) に移した。SCX を CHCl<sub>3</sub>/MeOH (1/1) 混合溶液 (5 mL) で洗浄し、2N-NH<sub>3</sub>/MeOH 溶液 (5 mL) で溶出した。溶出液を濃縮し、HPLC 分取システムにより精製を行ない、2, 4-ジクロロ-6-[(4-{[(6-クロロ(1, 4-ジヒドロキナゾリン-2-イル))アミノ]メチル}ピペリジル)メチル]フェノールを得た。

収量 2. 3 mg、収率 19%、 $M+1=453.0$ 。

[実施例 4-6、4-8～4-11]

化合物番号 4-6、4-8～4-11 の化合物を、それぞれ対応する反応物を用いて、実施例 4-2 の方法に従い合成した。結果を表 17 に示す。

表 17

化合物 No.4-	収量(mg)	収率(%)	MW	M+1
1	3.6	10	402.2	403.2
2	2.7	16	418.1	419.0
3	7.7	50	384.1	385.1
4	1.0	7	384.1	385.1
5	6.6	61	362.2	363.2
6	2.6	25	502.1	503.1
7	2.3	19	452.1	453.0
8	1.4	3	432.2	433.1
9	6.3	12	436.1	437.1
10	2.1	4	432.2	433.1
11	2.8	6	434.1	435.1

2-[(4-ピペリジニルメチル)アミノ]ヒドロチオフェノ[3, 2, d]ピリミジン-4-オン誘導体の合成法

[参考例 5-1]

3-{[(フェニルカルボニルアミノ)チオキソメチル]アミノ}チオフェン-2-カルボン酸メチルエステルの合成

3-アミノチオフェン-2-カルボン酸メチルエステル (500 mg、3.18 mmol) のアセトン (3 mL) 溶液に、ベンゾイルイソチオシアネート (1038 mg、6.36 mmol) のアセトン (3 mL) 溶液を添加した。室温にて 10 時間攪拌、その後濃縮し、残渣をシリ

カゲルクロマトグラフィー (Hex/EtOAc = 10/1) により精製し、3- { [ (フェニルカルボニルアミノ) チオキソメチル] アミノ } チオフェン-2-カルボン酸メチルエステルを得た。

収量 866 mg、収率 85%、 $M+1 = 321.0$ 。

[参考例 5-2]

カリウムヒドロチオフェノ [3, 2, d] ピリミジン-4-オン-2-チオレート の合成

KOH (303 mg、5.4 mmol) の EtOH (10 mL) 溶液に、3- { [ (フェニルカルボニルアミノ) チオキソメチル] アミノ } チオフェン-2-カルボン酸メチルエステル (866 mg、2.7 mmol) の EtOH (3 mL) 溶液を添加した。加熱還流下 3 時間攪拌、析出した白色沈殿を濾取した。EtOH (5 mL × 2 回) で洗浄し、減圧下乾燥してカリウムヒドロチオフェノ [3, 2, d] ピリミジン-4-オン-2-チオレートを得た。

収量 476 mg、収率 79%。

NMR (DMSO- $d_6$ ) :  $\delta$  H 6.85 (m, 1H), 7.22 (m, 1H), 10.41 (br, 1H)

[参考例 5-3]

2-メチルチオヒドロチオフェノ [3, 2, d] ピリミジン-4-オンの合成

カリウムヒドロチオフェノ [3, 2, d] ピリミジン-4-オン-2-チオレート (476 mg、2.14 mmol) の水溶液 (10 mL) に、MeI (133  $\mu$ L、2.14 mmol) を添加した。室温にて 3 時間攪拌、析出した白色沈殿を濾取した。水 (5 mL × 2 回) で洗浄し、減圧下乾燥して、2-メチルチオヒドロチオフェノ [3, 2, d] ピリミジン-4-オンを得た。

収量 337 mg、収率 79%。

NMR (DMSO- $d_6$ ) :  $\delta$  H 2.49 (s, 1H), 7.26 (d,  $J=5.4$ , 1H), 8.08 (d,  $J=5.4$ , 1H)

[参考例 5-4]

2-[(1-Boc-4-ピペリジニルメチル) アミノ] ヒドロチオフエノ [3, 2, d] ピリミジン-4-オンの合成

2-メチルチオヒドロチオフエノ [3, 2, d] ピリミジン-4-オン 200 mg (1.0 mmol) のクロロホルム (5 mL) 溶液に、60%の3-クロロ過安息香酸 287 mg (1.0 mmol) を氷冷下に加え、室温にて2時間攪拌する。得られた溶液を濃縮し、化合物 1-Boc-4-アミノメチルピペリジン 235 mg (1.1 mmol)、トリエチルアミン 0.2 mL (1.5 mmol)、及び diglyme (diethylene glycol dimethyl ether) (5 mL) を加えた。得られた溶液を、180℃にて10時間攪拌、その後水 (10 mL) を加え、酢酸エチル (5 mL  $\times$  2回) にて抽出し、硫酸マグネシウムにて乾燥した。ろ過後、ろ液を濃縮し、残渣をシリカゲルクロマトグラフィー (Hex/EtOAc = 1/1  $\rightarrow$  0/1) にて精製し、2-[(1-Boc-4-ピペリジニルメチル) アミノ] ヒドロチオフエノ [3, 2, d] ピリミジン-4-オンを得た。

収量 160 mg、収率 44%。

LC/MS (LC/MSD) : (M+H) $^+$  = 365.1 (実測値)  
M = 364.16 (理論値)。

[参考例 5-5]

2-[(4-ピペリジニルメチル) アミノ] ヒドロチオフエノ [3, 2, d] ピリミジン-4-オンの合成

参考例 2-11 に従い、合成した。



収量 135 mg、収率 90%、 $M+1 = 265.1$ 。

[実施例 5-1]

化合物番号 5-1 の化合物を、参考例 5-1～5-5 によって合成した化合物を用いて、実施例 2-5 の方法に従い合成した。結果を表 18 に示す。

表 18

化合物 No.5-	収量(mg)	収率(%)	MW	M+1
1	17.0	42	438.0	439.0

5-メチル-2-[(4-ピペリジニルメチル)アミノ]ヒドロピロロ[3, 2, d]ピリミジン-4-オン誘導体の合成

[参考例 6-1]

5-メチル-2-[(4-ピペリジニルメチル)アミノ]ヒドロピロロ[3, 2, d]ピリミジン-4-オンの合成

参考例 5-1～5-5 に従い、3-アミノ-1-メチルピロロ-2-カルボン酸エチルエステルを原料に用いて合成し、表題化合物を得た。  
収量 245 mg、収率 92%、 $M+1 = 262.1$  (実測値)  $M = 261.1$  (理論値)。

[実施例 6-1]

化合物番号 6-1 の化合物を、参考例 6-1 によって合成した化合物を用いて、実施例 2-5 の方法に従い合成した。結果を表 19 に示す。

表 19

化合物 No.6-	収量(mg)	収率(%)	MW	M+1
1	4.0	11	436.3	436.1

2-[(4-ピペリジニルメチル)アミノ]-1H, 5H-ベンゾ[f]1, 3-ジアゼピン-4-オン誘導体の合成

## [参考例 7-1]

4- { [ ( { [2- (カルバモイルメチル) フェニル] アミノ} チオキソメチル) アミノ] メチル} ピペリジンカルボン酸 *tert* ブチルエステルの合成

1-N-Boc-4-アミノメチルピペリジン (869 mg, 4.06 mmol) をアセトニトリル (10 mL) に溶解し、氷浴下でチオカルボニルジイミダゾール (794 mg, 4.46 mmol) 及びイミダゾール (82.9 mg, 1.22 mmol) のアセトニトリル溶液 (15 mL) を滴下して、室温で4時間攪拌した。これに2- (2-アミノフェニル) -アセトアミド (670 mg, 4.46 mmol) を加え、60℃で一晩攪拌した。反応液を減圧濃縮した残渣をシリカゲルカラムクロマトグラフィー (塩化メチレン/メタノール=65:1→49:1) で精製して表題化合物を得た。

収量 1.41 g、収率 85%、 $M+1=407.2$  (実測値)  $M=406.2$  (理論値)。

## [参考例 7-2]

4- { [ (4-オキソ-1H、5H-ベンゾ [f] 1,3-ジアゼピン-2-イル) アミノ] メチル} ピペリジンカルボン酸 *tert* ブチルエステルの合成

4- { [ ( { [2- (カルバモイルメチル) フェニル] アミノ} チオキソメチル) アミノ] メチル} ピペリジンカルボン酸 *tert* ブチルエステル (410 mg, 1.01 mmol) をテトラヒドロフラン (15 mL) に溶解し、N, N'-ジシクロヘキシルカルボジイミド (208 mg, 1.01 mmol) を加え、室温で6時間攪拌した。不溶物を濾別して得られた濾液を減圧濃縮後、*n*-ヘキサン:酢酸エチル=1:2の溶液 (3 mL) に懸濁した。再度不溶物を濾別し、濾液を減

圧濃縮した残渣をシリカゲルカラムクロマトグラフィー（*n*-ヘキサン／酢酸エチル＝2／3→1／2）で精製して表題化合物を得た。収量193mg、収率51%。

$^{13}\text{C}$ -NMR（100MHz,  $\text{CDCl}_3$ ）： $\delta$ ＝156.6, 155.0, 136.1, 129.6, 129.2, 126.6, 126.2, 117.9, 79.7, 45.6, 36.7, 29.7, 28.5, 20.5

$^1\text{H}$ -NMR（400MHz,  $\text{CDCl}_3$ ）： $\delta$ ＝7.38（1H, d,  $J$ ＝7.3Hz）, 7.18－7.32（3H, m）, 7.14（1H, s）, 5.43（1H, s）, 4.07（2H, s）, 3.71（2H, s）, 3.06（1H, s）, 2.65（2H, m）, 1.61（3H, m）, 1.48（9H, s）, 1.05（2H, m）

〔参考例7－3〕

2－〔（4－ピペリジニルメチル）アミノ〕－1H, 5H－ベンゾ  
〔f〕1, 3－ジアゼピン－4－オン合成

参考例2－11に従い、4－{〔（4－オキソ－1H, 5H－ベンゾ  
〔f〕1, 3－ジアゼピン－2－イル）アミノ〕メチル}ピペリジんカルボン酸 *tert* ブチルエステルを原料に用いて、表題化合物を合成した。

収量218mg、収率定量的、 $M+1=273.1$ （実測値） $M=272.2$ （理論値）。

〔実施例7－1〕

化合物番号7－16および7－504の化合物を、参考例7－1～7－3によって合成した化合物に対して、対応する反応物を用いて、実施例2－5の方法に従い合成した。結果を表20に示す。

表20

化合物 No.7-	収量(mg)	収率(%)	MW	M+1
16	4.0	10	447.4	447.1
504	6.0	16	430.9	431.1

〔2-〔(4-ピペリジルメチル)アミノ〕ヒドロキナゾリン-4-オンの誘導体の合成

〔実施例 8-16〕

2-〔(〔1-〔(3, 5-ジクロロ-2-ヒドロキシーフェニル)メチル〕-4-ピペリジル〕メチル)アミノ〕ヒドロキナゾリン-4-チオンの合成

磁気攪拌子を備えた 15 mL なすフラスコに化合物番号 2-16 を 5.7 mg (0.0132 mmol) を入れ、オキシ塩化リン 1 g に溶解してバス温 120℃ 上で 1 時間攪拌した。減圧濃縮によりオキシ塩化リンを留去したのち、チオ尿素 84.2 mg (1.106 mmol) と 1, 4-ジオキサン 4 mL を加えて 1 時間還流させた。一旦溶媒を留去した後、残渣をメタノールに懸濁させ、SCX カラムにて固相抽出処理をおこない、2 M アンモニア/メタノール溶液で溶出させた溶出液を濃縮し、分取 HPLC で精製した。目的物を含むフラクションを濃縮し、無色粉末状の 2-〔(〔1-〔(3, 5-ジクロロ-2-ヒドロキシーフェニル)メチル〕-4-ピペリジル〕メチル)アミノ〕ヒドロキナゾリン-4-チオンを得た。結果を表 21 に示す。

表 21

化合物 No.8-	収量(mg)	収率(%)	MW	M+1
16	0.6	10	449.4	449.1

〔実施例 9〕

エオタキシンにより惹起される CCR3 発現細胞の細胞内カルシウム濃

## 度上昇に対する被験化合物の阻害能の測定

CCR3を安定して発現するK562細胞を用いて、細胞内カルシウム濃度上昇に対する本発明による化合物の阻害能を次の方法にて測定した。

CCR3発現K562細胞を、10mMHEPES (N-[2-hydroxyethyl] piperazine-N'-[2-ethanesulfonic acid]、ギブコBRL社製) 含有HBSS溶液 (Hanks' Balanced Salt Solution、ギブコBRL社製) に懸濁したものに、最終濃度が1  $\mu$ Mとなるように1mM Fura2アセトキシメチルエステル (同仁化学社製) を加え、37℃にて30分間インキュベートした。細胞を洗浄後、被験化合物と同時に96穴ホワイトプレート (ファルコン製) に添加し、5分後にアゴニストを添加し、これを340nmと380nmで励起し、340/380比をモニターすることにより、細胞内カルシウム濃度を測定した。アゴニストとしてヒトエオタキシン (ゼンザイム・テクネ社製) (0.5  $\mu$ g/ml) を用いた。被験化合物の阻害能は、エオタキシンの刺激する5分前に、CCR3発現K562細胞を被験化合物で処理した時の、細胞内カルシウム濃度を測定し、下記の式により抑制率 (%) を算出した。

$$\text{抑制率 (\%)} = \{ 1 - (A - B) / (C - B) \} \times 100$$

(A : 被験化合物で処理した後エオタキシンの刺激したときの細胞内カルシウム濃度、B : 無刺激のときの細胞内カルシウム濃度、C : 被験化合物で処理せずにエオタキシンの刺激したときの細胞内カルシウム濃度)

本発明のピペリジン誘導体の阻害能を測定したところ、例えば、下記の化合物番号で表す化合物は、10  $\mu$ M又は2  $\mu$ Mの下記化合物の濃

度において、それぞれ20～50%、50%～80%、又は80%以上の阻害能を示した。

10  $\mu$ Mの濃度で20%～50%の阻害能を示した化合物：

化合物番号No 1-：1-7、1-9、2-5、2-6、2-8、2-12、2-13、2-15、2-16、2-18、2-21、2-22、2-24、2-29、2-31、2-35、2-43、2-45、2-48、2-56、2-70、2-71、2-77、2-85、2-96、2-100～2-103、2-107、2-108、2-116、2-128、2-129、2-136、2-141、2-146、2-147、2-176～2-180、3-8、3-55、3-56、3-58、5-37、5-98、5-104、5-113、5-118、5-122、5-125、5-127、5-141、6-4～6-6、6-8

10  $\mu$ Mの濃度において50%～80%の阻害能を示した化合物：

化合物番号No 1-：1-3～1-6、1-10、1-11、2-2～2-4、2-23、2-30、2-33、2-34、2-39、2-41、2-42、2-47、2-49、2-51、2-54、2-57、2-60、2-61、2-64～2-66、2-73、2-80～2-82、2-84、2-89～2-91、2-95、2-106、2-109、2-112、2-113、2-115、2-120、2-122、2-123、2-127、2-130、2-133、2-134、2-137、2-138、2-142、2-142、2-170、2-173～2-175、3-7、3-9、4-29、5-20、5-21、5-30、5-36、5-39、5-40、5-42～5-45、5-49、5-65、5-72、5-96、5-97、5-99、5-101～5-103、5-108、5-109、5-111、5-115、

5-117、5-119、5-121、5-128~5-130、5-134、5-135、5-137~5-139、5-142、5-147、5-148、5-154~5-158、5-167、5-168、5-174、5-175、5-180、5-181、5-183

化合物番号No 2- : 2~4

10  $\mu$ Mの濃度で80%以上の阻害能を示した化合物:

化合物番号No 1- : 1-1、1-8、2-1、2-14、2-36~2-38、2-40、2-50、2-52、2-72、2-75、2-98、2-117~2-119、2-121、2-124~2-126、2-131、2-149~2-151、2-153、2-154、3-2、3-13、3-15、3-17、3-18、3-21~3-23、3-25、3-26、3-28~3-30、3-32~3-38、3-42~3-52、3-59、3-61、3-62、5-22~5-29、5-31~5-35、5-38、5-41、5-46~5-48、5-50~5-64、5-66~5-71、5-88~5-93、5-95、5-107、5-110、5-114、5-116、5-120、5-123、5-124、5-126、5-131~5-133、5-136、5-140、5-143~5-146、5-149~5-153、5-159~5-166、5-169~5-173、5-176~5-179、5-182、6-7、6-9、6-11~6-13、6-15

化合物番号No 2- : 1

化合物番号No 4- : 1

2  $\mu$ Mの濃度で20%~50%の阻害能を示した化合物:

化合物番号No 1- : 2-156~2-159、2-163、2-164、3-14、3-24、3-27、3-40、4-1、4-3、4-

4、4-6、5-15、5-16、5-74、5-75、5-77、5-79、5-82、5-84、5-85

化合物番号No2-: 5、7、8、13、22、24、200、232、243、245、247、

2  $\mu$ Mの濃度で50%~80%の阻害能を示した化合物:

化合物番号No1-: 2-166、2-168、2-169、3-4、3-11、3-16、3-31、4-12、4-15~4-17、5-7、5-8、5-14、5-19、5-73、5-76、5-78、5-80、5-81、5-83、5-86、5-188

化合物番号No2-: 6、10、14、16、17、20、21、23、29、196、205、221、223、224、234、237、244、495

化合物番号No4-: 5

化合物番号No7-: 504

2  $\mu$ Mの濃度で80%以上の阻害能を示した化合物:

化合物番号No1-: 2-160、2-162、2-165、2-167、3-1、3-3、3-5、3-6、4-10、4-11、4-13、4-14、4-18~4-21、5-1~5-6、5-9~5-13、5-17、5-18、5-184~5-187、5-189、5-190

化合物番号No2-: 11、12、15、18、19、26~28、30、186~195、197~199、201~204、206~220、225~231、235、236、238~242、246、248~250、499、511、513、565

化合物番号No3-: 1~10、208、220、223、235、238、368、504、505、511、523、525、526、5



27、555、577

化合物番号No 4- : 2~4、6~11

化合物番号No 6- : 1

化合物番号No 7- : 16, 504

化合物番号No 8- : 16

[実施例10]

CCR3発現細胞へのエオタキシンの結合に対する阻害能の測定

ヒトCCR3発現L1.2細胞を、アッセイバッファー[RPMI 1640 (phenol red free), 25mM HEPES (pH 7.4), 0.1% NaN<sub>3</sub>, 0.1% gelatin, 0.08% CHAPS]に懸濁し、 $5 \times 10^5$ 個/mLの全細胞懸濁液とした。被験化合物をアッセイバッファーで希釈した溶液を、被験化合物溶液とした。 [<sup>125</sup>I] 標識ヒトエオタキシン (アマシャム社製) を、1  $\mu$ Ci/mLになるようにアッセイバッファーで希釈した溶液を標識リガンド溶液とした。0.5% BSAで被覆した96ウェルマイクロプレート (ファルコン社製) に、1ウェルあたり、被験化合物溶液25  $\mu$ L、標識リガンド溶液25  $\mu$ L、全細胞懸濁液50  $\mu$ Lの順番に分注し、攪拌後 (反応溶液100  $\mu$ L)、25℃で90分間インキュベートした。

反応終了後、あらかじめ0.5% ポリエチレンイミン溶液にフィルターを浸漬した96ウェルフィルタープレート (ミリポア社製) で、反応液をフィルター濾過し、フィルターを冷洗浄バッファー (アッセイバッファー+0.5M NaCl) 150  $\mu$ Lで、4回洗浄した (冷洗浄バッファー150  $\mu$ Lを加えて、濾過した)。フィルターを風乾後、液体シンチレーター (MicroScient-O、パッカード社製) を、1ウェルあたり25  $\mu$ Lずつ加え、フィルター上の膜画分が保持

する放射能をトップカウント（パッカー社製）にて測定した。

被験化合物の代わりに非標識ヒトエオタキシン 100 ng を添加した時のカウントを非特異的吸着として差し引き、被験化合物を何も添加しない時のカウントを 100 % として、ヒトエオタキシンの CCR3 発現細胞への結合に対する被験化合物の阻害能を算出した。

$$\text{阻害率 (\%)} = \{ 1 - (A - B) / (C - B) \} \times 100$$

(A : 被験化合物添加時のカウント、B : 非標識ヒトエオタキシン 100 ng 添加時のカウント、C : [ $^{125}$ I] 標識ヒトエオタキシンのみ添加した時のカウント)

#### [実施例 11]

エオタキシンにより惹起される CCR3 発現細胞の細胞遊走に対する被験化合物の阻害能の測定

CCR3 レセプターを安定して発現する L1.2 細胞を用いて、細胞遊走能に対する本発明における化合物の阻害能を次の方法にて測定した。

被検化合物を、0.5 % BSA 含有 RPMI 1640 (ギブコ BRL 社製) 溶液に懸濁したものに、アゴニストとしてヒトエオタキシン (ゼンザイム・テクネ社製) (20 ng/mL) を加えたものを、96 穴ケモタキシス・チャンバー (ニューロ・プローブ社製) の下層に入れ、ケモタキシス・チャンバー専用フィルターを上層チャンバーではさみこむようにしてセットした。上層チャンバーにも同じ被検化合物及び CCR3 発現 L1.2 細胞を添加したのち、37℃ で 2 時間インキュベートした。反応終了後、鑑別用血液染色液 (ディフ・クイック、国際試薬社製) で専用フィルターを染色し、550 nm の吸光度の測定を行い、下記の式にて抑制率 (%) を算出した。

$$\text{抑制率 (\%)} = \{ 1 - (A - B) / (C - B) \} \times 100$$

(A : 被験化合物で処理された CCR3 発現 L1.2 細胞をエオタキシ

ンで刺激したときの細胞遊走能、B：無刺激状態における細胞遊走能、  
C：被験化合物で処理せずにエオタキシンで刺激したときの細胞遊走能)

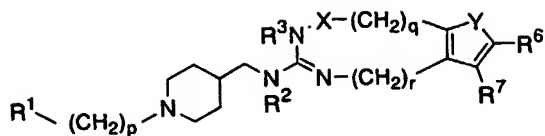
実施例 10、11 において、本発明の化合物のいくつかを被験化合物として測定したところ、その阻害能は、それぞれ実施例 9 のものと本質的に同じであった。

#### 産業上の利用可能性

本発明の式 (I) で表される化合物は、エオタキシン等の CCR3 のリガンドが標的細胞に結合することを阻害する活性、及びエオタキシン等の CCR3 のリガンドの標的細胞への生理的作用を阻害する活性を有し、CCR3 拮抗剤として利用できる。

## 請求の範囲

## 1. 下記式 (I)



(I)

[式中、 $R^1$ はフェニル基、 $C_3 \sim C_8$ シクロアルキル基、又は芳香族複素環基（ヘテロ原子として酸素原子、硫黄原子、及び窒素原子からなる群から選ばれる原子を1～3個有する。）を表わし、

$R^1$ におけるフェニル基又は芳香族複素環基は、ベンゼン環又は芳香族複素環基（ヘテロ原子として酸素原子、硫黄原子、及び窒素原子からなる群から選ばれる原子を1～3個有する。）と縮合して縮合環を形成してもよく、

$R^1$ におけるフェニル基、 $C_3 \sim C_8$ シクロアルキル基、芳香族複素環基、又は縮合環は、無置換或いはハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、カルボキシ基、 $C_1 \sim C_6$ アルキル基、 $C_3 \sim C_8$ シクロアルキル基、 $C_2 \sim C_6$ アルケニル基、 $C_1 \sim C_6$ アルコキシ基、 $C_1 \sim C_6$ アルキルチオ基、 $C_3 \sim C_5$ アルキレン基、 $C_2 \sim C_4$ アルキレンオキシ基、 $C_1 \sim C_3$ アルキレンジオキシ基、フェニル基、フェノキシ基、フェニルチオ基、ベンジル基、ベンジルオキシ基、ベンゾイルアミノ基、ホルミル基、 $C_2 \sim C_7$ アルカノイル基、 $C_2 \sim C_7$ アルコキシカルボニル基、 $C_2 \sim C_7$ アルカノイルオキシ基、 $C_2 \sim C_7$ アルカノイルアミノ基、 $C_1 \sim C_6$ アルキルスルホニル基、 $C_3 \sim C_8$ （アルコキシカルボニル）メチル基、アミノ基、モノ（ $C_1 \sim C_6$ アルキル）アミノ基、ジ（ $C_1 \sim C_6$ アルキル）アミノ基、カルバモイル基、 $C_2 \sim C_7$ N-アルキルカルバモイル基、 $C_4 \sim C_9$ N-シクロアルキルカルバモイル基、

N-フェニルカルバモイル基、ピペリジルカルボニル基、モルホリニルカルボニル基、ピロリジニルカルボニル基、ピペラジニルカルボニル基、N-メトキシカルバモイル基、(ホルミル)アミノ基、及びウレイド基からなる群から選ばれる1個以上の置換基で置換されてもよく、

$R^1$ のフェニル基、 $C_3 \sim C_8$ シクロアルキル基、芳香族複素環基、又は縮合環の置換基は、無置換或いは $C_1 \sim C_6$ アルキル基、 $C_2 \sim C_6$ アルケニル基、 $C_2 \sim C_6$ アルキニル基、フェニル基、 $C_3 \sim C_5$ アルキレン基、 $C_3 \sim C_8$ シクロアルキル基、 $C_3 \sim C_8$ シクロアルケニル基、 $C_1 \sim C_6$ アルコキシ基、 $C_1 \sim C_6$ アルキルチオ基、アミノ基、モノ( $C_1 \sim C_6$ アルキル)アミノ基、ジ( $C_1 \sim C_6$ アルキル)アミノ基、ピロリジニル基、ピペリジル基、 $C_3 \sim C_7$ ラクタム基、カルバモイル基、 $C_2 \sim C_7$ N-アルキルカルバモイル基、 $C_2 \sim C_7$ アルコキシカルボニル基、カルボキシル基、ヒドロキシ基、ベンゾイル基、シアノ基、トリフルオロメチル基、ハロゲン原子、及びtert-ブトキシカルボニルアミノ基からなる群から選ばれる1個以上の置換基によって置換されていてもよい。

ただし、 $R^1$ が $C_3 \sim C_8$ シクロアルキル基の場合、その置換基としてアミノ基、モノ( $C_1 \sim C_6$ アルキル)アミノ基、又はジ( $C_1 \sim C_6$ アルキル)アミノ基を含まない。

pは、1～6の整数を表す。

$R^2$ 及び $R^3$ は、同一又は異なって、それぞれ独立に、水素原子、 $C_1 \sim C_6$ アルキル基、又はフェニル基を表わし、

$R^2$ 及び $R^3$ における $C_1 \sim C_6$ アルキル基又はフェニル基は、無置換或いはハロゲン原子、ヒドロキシ基、 $C_1 \sim C_6$ アルキル基、 $C_2 \sim C_7$ アルコキシカルボニル基、アミノ基、カルバモイル基、カルボキシル基、シアノ基、及び $C_1 \sim C_6$ アルコキシ基からなる群から選ばれる1個以

上の置換基によって置換されてもよい。

Xは、 $-\text{CO}-$ 、 $-\text{SO}_2-$ 、 $-\text{CH}_2-$ 、 $-\text{CS}-$ 、又は単結合を表す。

qは、0又は1を表す。

rは、0又は1を表す。

Yは、 $-(\text{R}^4)\text{C}=\text{C}(\text{R}^5)-$ 、 $-\text{S}-$ 、又は $-\text{NR}^8-$ を表す。

$\text{R}^4$ 、 $\text{R}^5$ 、 $\text{R}^6$ 及び $\text{R}^7$ は、同一又は異なって、それぞれ独立に、水素原子、ハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、カルボキシル基、 $\text{C}_1\sim\text{C}_6$ アルキル基、 $\text{C}_3\sim\text{C}_8$ シクロアルキル基、 $\text{C}_2\sim\text{C}_6$ アルケニル基、 $\text{C}_1\sim\text{C}_6$ アルコキシ基、 $\text{C}_1\sim\text{C}_6$ アルキルチオ基、 $\text{C}_3\sim\text{C}_5$ アルキレン基、 $\text{C}_2\sim\text{C}_4$ アルキレンオキシ基、 $\text{C}_1\sim\text{C}_3$ アルキレンジオキシ基、フェニル基、フェノキシ基、フェニルチオ基、フェニルスルフォニル基、ベンジル基、ベンジルオキシ基、ベンゾイルアミノ基、ホルミル基、 $\text{C}_2\sim\text{C}_7$ アルカノイル基、 $\text{C}_2\sim\text{C}_7$ アルコキシカルボニル基、 $\text{C}_2\sim\text{C}_7$ アルカノイルオキシ基、 $\text{C}_2\sim\text{C}_7$ アルカノイルアミノ基、 $\text{C}_4\sim\text{C}_{10}$ シクロアルカノイルアミノ基、 $\text{C}_3\sim\text{C}_7$ アルケノイルアミノ基、 $\text{C}_1\sim\text{C}_6$ アルキルスルホニル基、 $\text{C}_1\sim\text{C}_6$ アルキルスルホニルアミノ基、 $\text{C}_3\sim\text{C}_8$ （アルコキシカルボニル）メチル基、アミノ基、モノ（ $\text{C}_1\sim\text{C}_6$ アルキル）アミノ基、ジ（ $\text{C}_1\sim\text{C}_6$ アルキル）アミノ基、カルバモイル基、 $\text{C}_2\sim\text{C}_7\text{N}$ -アルキルカルバモイル基、 $\text{C}_4\sim\text{C}_9\text{N}$ -シクロアルキルカルバモイル基、 $\text{N}$ -フェニルカルバモイル基、 $\text{N}$ -（ $\text{C}_7\sim\text{C}_{12}$ フェニルアルキル）カルバモイル基、ピペリジルカルボニル基、モルホリニルカルボニル基、ピロリジニルカルボニル基、ピペラジニルカルボニル基、 $\text{N}$ -メトキシカルバモイル基、スルファモイル基、 $\text{C}_1\sim\text{C}_6\text{N}$ -アルキルスルファモイル基、（ホルミル）アミノ基、（チオホルミル）アミノ基、ウレイド基、又はチオウ

レイド基を表し、

$R^4$ 、 $R^5$ 、 $R^6$ 及び $R^7$ の前記基は、それぞれ独立に、無置換或いは $C_1 \sim C_6$ アルキル基、 $C_2 \sim C_6$ アルケニル基、 $C_2 \sim C_6$ アルキニル基、フェニル基、 $C_3 \sim C_5$ アルキレン基、 $C_3 \sim C_8$ シクロアルキル基、 $C_3 \sim C_8$ シクロアルケニル基、 $C_1 \sim C_6$ アルコキシ基、( $C_1 \sim C_6$ アルコキシ)( $C_1 \sim C_6$ アルコキシ)基、フェニル( $C_1 \sim C_6$ アルコキシ)基、 $C_1 \sim C_6$ アルキルチオ基、アミノ基、モノ( $C_1 \sim C_6$ アルキル)アミノ基、ジ( $C_1 \sim C_6$ アルキル)アミノ基、ピロリジニル基、ピペリジル基、( $C_2 \sim C_7$ アルカノイル)ピペリジル基、 $C_3 \sim C_7$ ラクタム基、カルバモイル基、 $C_2 \sim C_7$ N-アルキルカルバモイル基、 $C_4 \sim C_9$ N-シクロアルキルカルバモイル基、N-フェニルカルバモイル基、N-( $C_7 \sim C_{12}$ フェニルアルキル)カルバモイル基、 $C_2 \sim C_7$ アルカノイルアミノ基、 $C_2 \sim C_7$ アルコキシカルボニル基、カルボキシル基、ヒドロキシ基、ベンゾイル基、シアノ基、トリフルオロメチル基、ハロゲン原子、tert-ブトキシカルボニルアミノ基、 $C_1 \sim C_6$ アルキルスルホニル基、及び複素環若しくは芳香族複素環(複素環若しくは芳香族複素環は、ヘテロ原子として酸素原子、硫黄原子、及び窒素原子からなる群から選ばれる原子を1~3個有し、 $C_1 \sim C_6$ アルキル基で置換されてもよい。)からなる群から選ばれる1個以上の置換基によって置換されていてもよい。

$R^8$ は、水素原子又は $C_1 \sim C_6$ アルキル基を表わし、

$R^8$ における $C_1 \sim C_6$ アルキル基は、無置換或いはハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、カルボキシル基、カルバモイル基、メルカプト基、グアニジノ基、 $C_3 \sim C_8$ シクロアルキル基、 $C_1 \sim C_6$ アルコキシ基、 $C_1 \sim C_6$ アルキルチオ基、フェニル基(フェニル基は、無置換或いはハロゲン原子、ヒドロキシ基、 $C_1 \sim C_6$ アルキル基、 $C_1$

～C<sub>6</sub>アルコキシ基、及びベンジルオキシ基からなる群から選ばれる1個以上の置換基によって置換されていてもよい。)、フェノキシ基、ベンジルオキシ基、ベンジルオキシカルボニル基、C<sub>2</sub>～C<sub>7</sub>アルカノイル基、C<sub>2</sub>～C<sub>7</sub>アルコキシカルボニル基、C<sub>2</sub>～C<sub>7</sub>アルカノイルオキシ基、C<sub>2</sub>～C<sub>7</sub>アルカノイルアミノ基、C<sub>2</sub>～C<sub>7</sub>N-アルキルカルバモイル基、C<sub>2</sub>～C<sub>6</sub>アルキルスルホニル基、アミノ基、モノ(C<sub>1</sub>～C<sub>6</sub>アルキル)アミノ基、ジ(C<sub>1</sub>～C<sub>6</sub>アルキル)アミノ基、及びウレイド基からなる群から選ばれる1個以上の置換基によって置換されていてもよい。]

で表される化合物、その薬学的に許容される酸付加体、又はその薬学的に許容されるC<sub>1</sub>～C<sub>6</sub>アルキル付加体。

2. 前記式(I)において、Xが-SO<sub>2</sub>-である請求の範囲第1項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容されるC<sub>1</sub>～C<sub>6</sub>アルキル付加体。

3. 前記式(I)において、Xが-CO-である請求の範囲第1項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容されるC<sub>1</sub>～C<sub>6</sub>アルキル付加体。

4. 前記式(I)において、Xが-CH<sub>2</sub>-である請求の範囲第1項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容されるC<sub>1</sub>～C<sub>6</sub>アルキル付加体。

5. 前記式(I)において、Xが-CS-である請求の範囲第1項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容されるC<sub>1</sub>～C<sub>6</sub>アルキル付加体。

6. 前記式(I)において、Xが単結合である請求の範囲第1項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容されるC<sub>1</sub>～C<sub>6</sub>アルキル付加体。



7. 前記式 (I) において、Y が  $-(R^4)C=C(R^5)-$  である請求の範囲第 1 項～第 6 項のいずれか 1 項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体。

8. 前記式 (I) において、Y が  $-S-$  である請求の範囲第 1 項～第 6 項のいずれか 1 項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体。

9. 前記式 (I) において、Y が  $-NR^8-$  である請求の範囲第 1 項～第 6 項のいずれか 1 項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体。

10. 前記式 (I) において、 $R^1$  が置換もしくは無置換のフェニル基である請求の範囲第 1 項～第 9 項のいずれか 1 項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体。

11. 前記式 (I) において、 $R^2$  が水素原子である請求の範囲第 1 項～第 10 項のいずれか 1 項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体。

12. 前記式 (I) において、 $R^3$  が水素原子である請求の範囲第 1 項～第 11 項のいずれか 1 項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体。

13. 前記式 (I) において、 $q = 0$  であり、かつ  $r = 0$  である請求の範囲第 1 項～第 12 項のいずれか 1 項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体。

14. 前記式 (I) において、 $q = 1$  であり、かつ  $r = 0$  である請求の範囲第 1 項～第 12 項のいずれか 1 項に記載の化合物、その薬学的に許

容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体。

15. 前記式 (I) において、 $q = 0$  であり、かつ  $r = 1$  である請求の範囲第1項～第12項のいずれか1項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体。

16. 前記式 (I) において、 $p = 1$  である請求の範囲第1項～第15項のいずれか1項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体。

17. 前記式 (I) において、Yが  $-(R^4)C=C(R^5)-$  であり、 $R^1$  が置換もしくは無置換のフェニル基であり、 $R^2$  が水素原子であり、 $R^3$  が水素原子であり、 $q = 0$  であり、 $r = 0$  であり、 $p = 1$  である請求の範囲第2項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体。

18. 前記式 (I) において、Yが  $-(R^4)C=C(R^5)-$  であり、 $R^1$  が置換もしくは無置換のフェニル基であり、 $R^2$  が水素原子であり、 $R^3$  が水素原子であり、 $q = 0$  であり、 $r = 0$  であり、 $p = 1$  である請求の範囲第3項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体。

19. 前記式 (I) において、Yが  $-(R^4)C=C(R^5)-$  であり、 $R^1$  が置換もしくは無置換のフェニル基であり、 $R^2$  が水素原子であり、 $R^3$  が水素原子であり、 $q = 0$  であり、 $r = 0$  であり、 $p = 1$  である請求の範囲第4項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体。

20. 前記式 (I) において、Yが  $-(R^4)C=C(R^5)-$  であり、 $R^1$  が置換もしくは無置換のフェニル基であり、 $R^2$  が水素原子であり、

$R^3$ が水素原子であり、 $q = 0$ であり、 $r = 0$ であり、 $p = 1$ である請求の範囲第6項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体。

21. 前記式(I)において、 $R^4$ 及び $R^5$ が、同一または異なって、それぞれ独立に、水素原子、ハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、カルボキシ基、 $C_1 \sim C_6$ アルキル基、 $C_1 \sim C_6$ アルコキシ基、 $C_2 \sim C_7$ アルコキシカルボニル基、 $C_2 \sim C_7$ アルカノイルアミノ基、 $C_1 \sim C_6$ アルキルスルホニル基、アミノ基、カルバモイル基、 $C_2 \sim C_7$ N-アルキルカルバモイル基、スルファモイル基、又は $C_1 \sim C_6$ N-アルキルスルファモイル基である請求の範囲第17項～第20項のいずれか1項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体。

22. 前記式(I)において、 $R^4$ 及び $R^5$ が、同一または異なって、それぞれ独立に、ハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、 $C_1 \sim C_6$ アルキル基、 $C_1 \sim C_6$ アルコキシ基、 $C_2 \sim C_7$ アルコキシカルボニル基、 $C_1 \sim C_6$ アルキルスルホニル基、又は $C_1 \sim C_6$ N-アルキルスルファモイル基、である請求の範囲第17項～第20項のいずれか1項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体。

23. 前記式(I)において、 $R^1$ が、同一または異なって、それぞれ独立に水素原子、ハロゲン原子、ヒドロキシ基、シアノ基、ニトロ基、 $C_1 \sim C_6$ アルキル基、又は $C_1 \sim C_6$ アルコキシ基である請求の範囲第17項～第22項のいずれか1項に記載の化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される $C_1 \sim C_6$ アルキル付加体。

24. 請求の範囲第1項～第23項のいずれか1項に記載の前記式(I)で表される化合物、その薬学的に許容される酸付加体、又はその

薬学的に許容される  $C_1 \sim C_6$  アルキル付加体を有効成分とする、CCR3 拮抗作用を有する医薬組成物。

25. 請求の範囲第1項～第23項のいずれか1項に記載の前記式(I)で表される化合物、その薬学的に許容される酸付加体、又はその薬学的に許容される  $C_1 \sim C_6$  アルキル付加体を有効成分とする、CCR3 が関与する疾患の予防及び／又は治療用組成物。

26. 前記疾患がアレルギー性疾患である請求の範囲第25項に記載の予防及び／又は治療用組成物。

27. 前記アレルギー性疾患が、気管支喘息、アレルギー性鼻炎、アトピー性皮膚炎、蕁麻疹、接触皮膚炎、又はアレルギー性結膜炎である請求の範囲第26項に記載の予防及び／又は治療用組成物。

28. 前記疾患が、炎症性腸疾患である請求の範囲第25項に記載の予防及び／又は治療用組成物。

29. 前記疾患が、エイズ（後天性免疫不全症候群）である請求の範囲第25項に記載の予防及び／又は治療用組成物。

30. 前記疾患が、好酸球増加症、好酸球性胃腸炎、好酸球増加性腸症、好酸球性筋膜炎、好酸球性肉芽腫、好酸球性膿疱性毛包炎、好酸球性肺炎、又は好酸球性白血病である請求の範囲第25項に記載の予防及び／又は治療用組成物。

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/04841

## A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl<sup>7</sup> C07D401/12, 401/14, 405/14, 409/14, 413/14, 417/14, 487/04, 495/04, A61K31/454, 31/4709, 31/5377, 31/5415, 31/4545, 31/517, A61P1/00, 11/00, 11/02, 17/00, 27/02, 29/00, 31/18, 37/08, 43/00, 11/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl<sup>7</sup> C07D401/12, 401/14, 405/14, 409/14, 413/14, 417/14, 487/04, 495/04, A61K31/454, 31/4709, 31/5377, 31/5415, 31/4545, 31/517, A61P1/00, 11/00, 11/02, 17/00, 27/02, 29/00, 31/18, 37/08, 43/00, 11/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAPLUS, REGISTRY (STN)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/25686 A1 (DUPONT PHARM. RES. LAB.), 27 May, 1999 (27.05.99), & AU 9913741 A & EP 1030840 A1 & NO 200002486 A & CZ 200001434 A & SK 200000553 A & HU 200004200 A & CN 1279668 A & BR 9814645 A & KR 2001032213 A & KR 2001032253 A & JP 2001-523661 A & NZ 503782 A	1-30
A	WO 00/53600 A1 (BANYU PHARM. CO., LTD.), 14 September, 2000 (14.09.00), & AU 200029420 A	1-30
A	WO 01/10439 A1 (TEIJIN LTD.), 15 February, 2001 (15.02.01), & AU 200063193 A & EP 1201239 A1 & KR 2002015722 A & CN 1376063 A	1-30

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search  
16 June, 2003 (16.06.03)

Date of mailing of the international search report  
01 July, 2003 (01.07.03)

Name and mailing address of the ISA/  
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/JP03/04841

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	WO 03/028641 A2 (TAISHO PHARM. CO., LTD.), 10 April, 2003 (10.04.03), (Family: none)	1-30

## A. 発明の属する分野の分類 (国際特許分類 (IPC))

Int. Cl<sup>7</sup> C07D401/12, 401/14, 405/14, 409/14, 413/14, 417/14, 487/04, 495/04, A61K31/454, 31/4709, 31/5377, 31/5415, 31/4545, 31/517, A61P1/00, 11/00, 11/02, 17/00, 27/02, 29/00, 31/18, 37/08, 43/00, 11/06

## B. 調査を行った分野

## 調査を行った最小限資料 (国際特許分類 (IPC))

Int. Cl<sup>7</sup> C07D401/12, 401/14, 405/14, 409/14, 413/14, 417/14, 487/04, 495/04, A61K31/454, 31/4709, 31/5377, 31/5415, 31/4545, 31/517, A61P1/00, 11/00, 11/02, 17/00, 27/02, 29/00, 31/18, 37/08, 43/00, 11/06

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で利用した電子データベース (データベースの名称、調査に使用した用語)  
CAPLUS, REGISTRY(STN)

## C. 関連すると認められる文献

引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
A	WO 99/25686 A1 (DUPONT PHARM. RES. LAB.) 1999. 05. 27 & AU 9913741 A & EP 1030840 A1 & NO 200002486 A & CZ 200001434 A & SK 200000553 A & HU 200004200 A & CN 1279668 A & BR 9814645 A & KR 2001032213 A & KR 2001032253 A & JP 2001-523661 A & NZ 503782 A	1-30
A	WO 00/53600 A1 (BANYU PHARM. CO., LTD.) 2000. 09. 14 & AU 200029420 A	1-30

☒ C欄の続きにも文献が列挙されている。☐ パテントファミリーに関する別紙を参照。

## \* 引用文献のカテゴリー

- 「A」 特に関連のある文献ではなく、一般的技術水準を示すもの  
「E」 国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの  
「L」 優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献 (理由を付す)  
「O」 口頭による開示、使用、展示等に言及する文献  
「P」 国際出願日前で、かつ優先権の主張の基礎となる出願

- の日の後に公表された文献  
「T」 国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの  
「X」 特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの  
「Y」 特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの  
「&」 同一パテントファミリー文献

国際調査を完了した日

16. 06. 03

国際調査報告の発送日

01.07.03

国際調査機関の名称及びあて先

日本国特許庁 (ISA/J P)

郵便番号 100-8915

東京都千代田区霞が関三丁目4番3号

特許庁審査官 (権限のある職員)

富永 保

4 P

9159

電話番号 03-3581-1101 内線 3490

C (続き) . 関連すると認められる文献		
引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
A	WO 01/10439 A1 (TEIJIN LTD.) 2001. 02. 15 & AU 200063193 A & EP 1201239 A1 & KR 2002015722 A & CN 1376063 A	1-30
PA	WO 03/028641 A2 (TAISHO PHARM. CO., LTD.) 2003. 04. 10 (ファミリーなし)	1-30